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PERIPHERAL PULSATIONS IN THE VEINS IN CONGESTIVE FAILURE OF THE HEART, ASSOCIATED WITH PULSATION OF THE LIVER AND TRICUSPID REGURGITATION *

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Our purpose is to offer a means of arriving at an early and more definite knowledge of cardiac incompetency by calling attention to certain well marked pulsations in the peripheral veins. These are especially pronounced in the median basilic vein of the forearm and in the veins on the dorsum of the hands, and they occurred in all of a series of more than fifty cases in which a diagnosis of cardiac failure and tricuspid insufficiency had been made on other clinical and anatomic grounds. A large number of compensated controls did not show these pulsations.

The relatively common occurrence of functional tricuspid insufficiency is not recognized by clinicians in general as often as it should be. This has been pointed out frequently by Mackenzie.[1] This fact was brought home to us when it was discovered that quite a large proportion of the average run of patients at our disposal in the medical and surgical wards had some degree of functional insufficiency though in the great majority of cases this was not suspected at the time. When this fact was determined and the patient was given supportive treatment, there was a decided improvement in prognosis.

Venous pulsations in the jugular veins is the subject of a large amount of literature. This literature deals in part with tricuspid insufficiency, its signs and symptoms in diagnosis, and in part with the interpretation of the graphic registration of venous pulsation. There are only a few isolated references to pulsations in the peripheral veins. These references have not been given proper prominence nor has their significance been recognized in relation to cardiac insufficiency. No single author, so far as we were able to ascertain, has ever definitely compiled a series of cases of venous pulsations in the peripheral veins with the idea of indicating their almost constant association with tricuspid insufficiency or their early appearance with the onset of congestive failure. Aside from their historical interest, these reports are

* From the Department of Medicine, University of California Medical School.

1. Mackenzie: Diseases of the Heart, 1914, p. 336.

valuable in that they are accurate descriptions of cases comparable to some that we have observed. We quote at some length from certain early articles.

HISTORICAL REVIEW

Davis [2] in 1827 (also cited by King and others) reported a case of "remarkable pulsations in the veins" as follows:

"June 21, 1826, Margaret Connor, aet. 6; emaciated; whooping cough four months previously with poor recovery; vomiting for last ten days. Pulse 88, slightly irregular, full and pretty strong; constipated; petechiae resembling purpura simplex and a miliary vesicular eruption on chest and neck."

"Pulsations in all the veins, distinct and well marked, synchronous with that of the arteries and in the veins of the extremities, perceptible to the eye even at a distance of 2 yards. The veins were rather larger than is usual at her period of life and pressure upon any of them stopped the pulsation between the point compressed and the heart, so that it obviously could not be caused by regurgitation from the auricle." Necropsy showed hydropericardium and "the left ventricle of the heart was somewhat enlarged and firmer than natural." The rest was normal. The arteries were injected and showed no enlarged communications with the veins and no arteries were found near these veins "which could throw a doubt on the fact that the pulsation had been continued through the arteries and capillaries to the veins."

Ward [3] in 1832 reported a "singular effect of castor oil."

A woman, aged 30, five months pregnant, had fever, cough and generalized pains, dyspnea, rapid pulse and exhaustion from catharsis and bleeding. Three days following miscarriage, Ward says, "she was sitting up, and I observed that the veins of her hands were greatly distended and pulsated with great violence. The skin being very pellucid, the pulse was very distinct in the small ramifications of the fingers, in which the blood was of the arterial color, the larger veins being darker but not so blue as usual. The pulsation extended beyond the middle of the forearm and was not stopped by pressure upon the veins at any point above, though it was stopped by pressure below the pulsating parts whether on fingers or back of hand." It was synchronous with the radial pulse which beat high. The pulsations continued for three days and gradually disappeared, after which there was some transitory edema of the legs. He thought that the "excessive reaction of the heart pushing the thin and impoverished blood through the capillaries right on into the veins" overcame the restrictions of the capillary bed.

Graves [4] (1833), cited by King, saw a patient with Dr. Ireland and Mr. Crampton. He says:

She had a violent attack of peritonitis and during the course of her illness we observed this leaping of the arteries, accompanied by a visible pulsation in the veins on the back of the hand; yet both entirely ceased when the inflammation subsided.

Benson [5] (1836), in a comprehensive paper, reported a case of venous pulsation in the upper extremities; on section he determined to

2. Davis: Dublin Hosp. Rep. **4**:272-275, 1827.
3. Ward: London M. Gaz. **10**:376, 1832.
4. Graves: London M. & S. J. **3**:77, 1833.
5. Benson: Dublin J. Med. & Chem. Sc. **8**:324-332, 1836.

his own satisfaction "that hypertrophy with dilatation of the right ventricle was the true cause." The following is a brief résumé of the case:

Mary Oliver, aged 60, was alcoholic, weak, pale and emaciated. There were marked pulsation of the heart and loud murmurs over all the precordia. She became comatose and pulsations were noted in "every superficial vein of the two upper extremities." The pulsations in the distended veins were synchronous with the radial pulsations though a little later. The veins of the trunk and lower extremities were motionless. The jugular and carotid veins beat vehemently. He says that the "internal jugulars became greatly distended and collapsed during each act of respiration, whilst a confused tremulous pulse incessantly agitated them." Venous section of 10 ounces (.295 c.c.) relieved the patient and caused the "pulsations to disappear. The blood did not come per saltum although pulsation was observed in some of the veins below the bandage." Four days later the pulsations returned.

"My colleagues and the hospital pupils now joined me in observing the pulsations and the veins were seen to rise and fall with respiration, becoming turgid towards the end of respiration and flaccid when inspiration was nearly complete. In both states, however, their pulsation went on regularly, beating as often as the artery, eighty in a minute, but a little after it. There was no doubt of this, though the interval was very minute." On venous section from the cephalic vein to obviate arterial pulsations, the blood "flowed distinctly per saltum. It was like arterial blood in color but of much thinner consistency." "After removal of eight ounces, the pulsations ceased." The patient died the next night.

Before section, there were two opinions as to the cause of the pulsating veins. These may be presented in full because they point out the situation as it stands today, and the proof that Benson offers for his contention holds equally well now. Furthermore, it is similar to that offered by us (some eighty-seven years later).

"First, that the pulsation was derived from the left side of the heart, sending on its blood through the capillaries into the veins; second, that it was derived from the right side of the heart, and depended on regurgitation." "In support of the former opinion, it was observed, first, that pressure on the brachial or subclavian arteries stopped the pulsation, but that it was unaffected by pressing on a vein; second, that the valves acted perfectly as could be seen by emptying a portion of vein just below a valve, and therefore that regurgitation was impossible; third, that the venous pulse occurred at such an interval after the arterial as was inconsistent with regurgitation, but might be expected if the blood had to travel round by the capillaries, and fourth, that the debilitated condition of the patient might have so relaxed the capillaries as to allow of an unusually free communication between the arteries and veins."

"In answer to these arguments and in favor of regurgitation, it was urged, first, that pressure on the brachial or subclavian arteries also acted more or less on the principal veins which accompanied them; besides by diminishing the quantity of fluid which the veins received, it would render their pulsation less evident, in the same way that the bleeding did; but that the free anastomosis would make amends for the slight interruption occasioned by pressing on a superficial vein; second, that though the valves acted well when the vein was emptied behind them, they would not prevent an impulse from being conveyed along the column of blood in a distended vessel; and that, in fact, if each valve were merely thrown suddenly across the venous tube, it would cause a venous pulse, though ever so perfect in its valvular function; third, that the yielding coats of the veins would serve to retard the rapidity of the returning wave and thus account for the momentary delay in their beat, and fourth, that the arterial pulse was not strong enough to justify us in supposing that it could be continued on to the veins; nor was there any ground for saying that the capillaries were relaxed."

At section, twelve hours after death, there were found generalized fibrous adhesions of the pleura; the lungs were free from disease and not even congested. The heart was markedly dilated and hypertrophied to twice the usual size. "The right auricle was dilated and a little hypertrophied. The right auriculoventricular opening was very large and gaping. The right ventricle was dilated and hypertrophied. Its cavity was twice as large and its walls twice as thick as usual. The floating margins of the tricuspid valves were thickened and studded with small cartilaginous nodules. The pulmonary valves were slightly thickened and the left auricle and ventricle slightly dilated and thickened. There was marked mitral stenosis with calcareous deposits. Thickened insufficient aortic valves. General atheroma. Abdominal viscera were healthy." The venous valves were competent; the weak left ventricle, in his opinion, could not have forced blood past the obstructions of the aortic valves and the calcareous aorta through the capillaries to cause the veins to pulsate. The pulse was not "from the right auricle, for their diastole always followed, though at an exceedingly short interval, the diastole of the arteries." It was not from the "coats of the veins . . . . nor in the neighboring arteries." He suggests that an hypertrophied right ventricle and a dilated auriculoventricular opening would allow regurgitation into the auricle of considerable force to communicate an impulse to the dilated veins "even to their small ramifications." The propagation of their impulse depended on the distended veins and not on the insufficiency of their valves. Benson points out that the interpretation of this and other cases reported (most of which are reviewed here) was fundamentally wrong and that "the dissection proved, I think, incontestably that hypertrophy with dilatation of the right ventricle was the true cause" (p. 331).

King[6] (1837), in his "Essay on the Safety Valve Function in the Right Ventricle of the Human Heart," makes several personal observations on pulsating veins. As these observations are unique, we are justified in quoting at some length. In his paragraph, "Venous Pulse in Health and Disease" (p. 107), he points out that on immersing the hand in warm water a venous pulsation equal in regularity and number if not synchronous with the arterial pulse can be seen in the cephalic vein. This pulsation causes an increase of the jet during venous section with each arterial pulsation. He suspects the capillary circulation of allowing the ventricular systole to penetrate to the veins (p. 106); i. e., "that the chief force is the ventricular impulse, through the arterial tubes and capillaries, into the veins of every part."

He says, "I was, some time since, surprised to find, that upon lying on my back in the sunlight, after dinner, the large mesian veins of my forehead were visibly pulsating. They are naturally of full size; and having become distended, a rather slow and slight diastole was seen, by the aid of a mirror, with or a little later than each temporal pulse." He naively explains in a footnote that he had had a moderate dinner "with one glass of porter and nearly as much water" one-half hour before. He repeated the observation and said, "Having taken water only, my veins still beat." Another time, while hungry, he found it necessary to elevate his feet to bring out the pulsation in the engorged veins. (This is rather an exposé of his appetite.)

6. King: Guy's Hosp. Rep. **2**:104-178, 1837.

To obviate the charge of the "will to see," he has had others beside himself verify these pulsations in several cases. . . . "On more than one occasion of unusual vascular excitement, I have also seen the dorsal veins of my own hands beating"—also of the leg and foot (p. 109). He affixed a waxed thread 2 inches (5 cm.) long with a little tallow to the veins of the hand and demonstrated the pulsations as differing markedly from the arterial beating. "In some veins, which, by a semirotation of the hand may be placed either in front or posteriorly, the effect has been the same;" i. e., he has tried to rule out the effect of an adjacent artery. By means of this capillary lever, he determined that the slow pulsations in a small superficial vein were manifestly later than the quick radial pulse.

In the pursuit of the same study, I was attending Dr. Bright in his visits to the wards of the hospital, and found two men with visibly pulsating veins on the backs of their hands. . . . The doctor not only saw, but thought he could feel, the venous diastole, the wrist being all the while embraced with some firmness to render the veins large. The patient had an hypertrophic heart and a very powerful pulse; his veins were rather few. In the second instance,

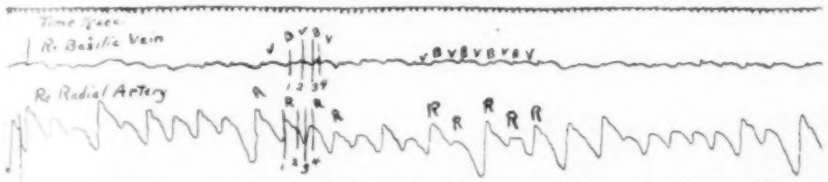


Fig. 1 (Case 1).—Tracings obtained with glass capsule on median basilic vein in mitral stenosis with fibrillation: 1, brachial and radial systole practically synchronous; *B*, wave transmitted from brachial artery similar to *C* wave in jugular pulse; 2, peak of venous pulsation in diastole of radial pulse; *V*, similar to *V* wave of jugular pulse; 3, end of venous pulsation and beginning of systole, and 4, beginning of venous pulsation at time of middle of radial systole (approximately one-fifth second after beginning of systole). In some tracings the brachial artery wave is absent. This is best shown when the skin is kept loose and the capsule applied as far from the pulsating artery as possible.

which was less marked, the man had had renal anasarca for sixteen days. His heart probably was not quite sound. The pulse was soft and tolerably good. He was perspiring profusely. The dorsal veins of the hands were pretty numerous and large and they were covered with abundance of hair, which was remarkable for the reason that the veins not only beat visibly in many places, but that particular hairs, which were well adapted for the purpose, seemed to form so many natural sphygmometers. It was here also necessary to enlarge the veins by gently grasping the wrist.

He cites the case of a girl, aged 11 years, with purpura and fever, during which, he says, "on very gently grasping the wrist in feeling the pulse, I observed for several days the numerous and rather full veins of the hand both prominent and beating. There was in all of them a very distinct diastole and systole." The patient died shortly after. The

lungs were edematous, the "heart's substance healthy," the blood watery. There were pale hypertrophic kidneys and suppuration of the parotid.

King was the first to compile the cases in which venous pulsations of the extremities had been previously noted. He says, "The earliest notice I have been able to find of a similar case is that which Haller (*Elementa Physiologiae*, T. II, p. 256) has quoted; and single instances have been more recently related by Steinbuch (*J.d. pract. Heilkunde*, September, 1815), in the *Philadelphia Journal* (Graves), by Sundelin (*Arch. f. Med. Erfahr.*, 1822), by Beyer (*J. Complimentaire*, T. XXI, 1825), by Davis [2] of Dublin, by Elliston (Blumenbach's Physiology, last edition), by Ward,[3] by Graves [4] (who indeed records two), and lastly by Benson." [5]

Bernard [7] (1862), during stimulation of the lingual nerve, noted that the blood vessels of the submaxillary gland dilated and the pulse could be seen in the capillaries and veins, and that the blood flowed from the veins bright and red and spurting, as if from an artery. This was probably a true relaxation of the capillary bed. Such a condition might occur in the superficial veins of the hands, etc., but usually with the venous congestion of tricuspid insufficiency there is a low blood pressure because of the weakened myocardium. They could arise from some vasomotor disturbance which should be found independently of tricuspid insufficiency.

Friedreich [8] (1866) noted simple pulsation of the left forehead and temple veins, vena cephalica antebrachii dextra, and the retinal veins in a case in which necropsy showed, besides other pathologic conditions, a dilated and large right heart with sclerotic, insufficient tricuspid valves. He suggested that tricuspid insufficiency in this case was first accompanied by a full and pulsating liver and later by the engorgement and reflux overcoming the venous valves, and that the pulsations appeared in the jugular bulb, the external jugular and finally in the vena cephalica antebrachii dextra. The vein valves were in good shape at necropsy. He considered liver pulsations as pathognomonic for tricuspid insufficiency. He saw pulsating veins on the forehead in a similar case in which on section a remarkable dilatation of the vena cava as well as a dilated right auricle were present.

He reviewed the literature thoroughly for venous pulsations in the extremities (p. 275), and cites observations of such pulsations by Hombert, Zuliani and Elliotson. He remarked that pulsations in the facial veins had not been mentioned before his two cases were reported. This is the first mention of pulsations in the retinal veins in this connection. He also cites Mavey, who, with Goubler and Verneuil, noted pulsation in varicose veins of one leg. In 1867, Friedreich [9] cited Walshe as having

7. Bernard: J. de Physiol. et Path. **5**:383-418, 1862; **1**:233, 649, 658, 1858.
8. Friedreich: Handb. d. spec. Path. u. Therap. **5**:192, 1867.
9. Friedreich: Deutsch. Arch. f. klin. Med. **1**:241-291, 1866.

noted pulsations in the vena mammaria. He thought the reason for the more common appearance of marked jugular pulsations on the right side was the position of the right innominate trunk.

Quincke [10] in 1868 described pulsating veins in the hands and feet of an anemic girl; the forearm and hands of a normal youth with a cord injury which had caused vasodilatation of the arms; a case of cholelithiasis in a woman, aged 50, with aortic insufficiency and hypertension; and on his own hands when the veins were dilated by heat. His criteria for seeing these pulsations are: a thin transparent skin free from edema and well filled veins that stand out well. He mentioned pulsations in the vena centralis retinae as commonly seen. In the case of vasodilatation the pulsations may well be transmitted from the arterioles as in Bernard's observation.

Friedreich [11] (1878) says, "Ich glaube den cruralvenenklappenton für ein ebenso sicheres Zeinchen für die Diagnose einer Insufficienz der Tricuspidal Klappe, betrachten zu können, als den früher von mir

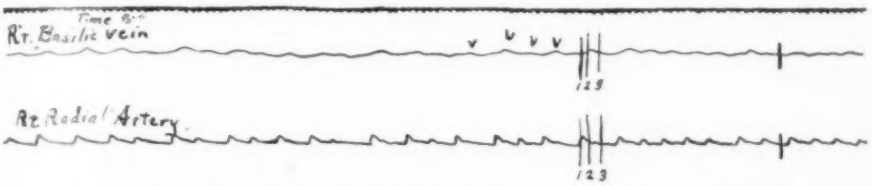


Fig. 2 (Case 1).—Tracing obtained with intravenous needle in median basilic vein: 1, beginning of radial systole; absence of brachial artery pulsation in absolutely smooth venous curves; tambour levers show only one pulsation: auricular waves are absent as fibrillation is present. 2, dicrotic notch just after the beginning of the venous wave; 3, end of radial pulse wave just before the end of the venous wave, with the summit between 2 and 3.

beschriebenen Lebervenenpuls." He describes several cases characteristic of mitral and tricuspid insufficiency, all of which showed the venous double tone in the "crural" vein and one of which presented a markedly pulsating median vein of the forearm. The first "crural" tone he thinks is due to the auricular systole and the second to ventricular reflux—they are accentuated and brought out by light pressure with the stethoscope.

Gerhardt [12] in 1894 noted a few pulsating veins over the manubrium in a case of mitral and tricuspid insufficiency with pulsating liver, pulsations in the crural veins and edema. In 1902 [13] he was of the opinion that diastolic collapse is occasionally seen in the small

10. Quincke: Berl. klin. Wchnschr. **34**:357, 1868.
11. Friedreich: Arch. f. klin. Med. **21**:205-258, 1878.
12. Gerhardt: Arch. f. exper. Path. u. Pharmakol. **34**:402-405, 1894.
13. Gerhardt: Arch. f. exper. Path. **47**:250-266, 1902.

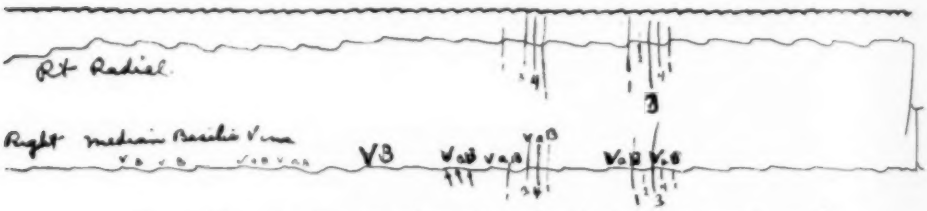
veins, i. e., external jugular, branches of the external mamillary and, seldom, the arm veins, while the great veins show systolic pulsation.

Gaertner [14] in 1903 frequently observed venous pulsations while reading venous pressures by his method.

Babcock [15] (1903), in his chapter on aortic regurgitation, spoke about a slow undulating venous pulse in the superior veins of the hand and forearm when they hang down so that the veins are turgid. This is especially prominent when arterial tension is low, as in fevers, anemia, etc.

Sewall [16] in 1906 stated that the veins of the forearm swell and contract with respiration and the pulse beat, and that a paper lever applied across them will show the oscillations.

Preble [17] in 1906 noted pulsations in the veins on the chest wall and upper arm in three patients with pernicious anemia who died soon afterward. The liver was not much enlarged. There was moderate dilatation of the heart and slight edema of the legs. No murmur was heard in any of the three cases.


Rt Radial
Right median Basilic Vein
V B
V B
V B

Pezzi and Gasperini [19] (1914) reported three cases with A and V waves in the liver and femoral vein tracings as characteristic of cases of tricuspid insufficiency.

Wilson,[20] in Nelson's System (1920), said that "the peripheral veins sometimes pulsate in exophthalmic goiter but venous pulsation is ordinarily confined to the internal and external jugular veins."

Hill [21] in 1921, in studying the pressures in the small arteries, capillaries and veins of a bat's wing, said, "A slow, rhythmic pulsation, as is well known, helps to maintain the flow in the veins of the bat's wing. This is little evident in the hot blooded state when the velocity of flow in the arteries and veins is very fast."

It would appear, therefore, that in offering our interpretation of pulsations in peripheral veins in a large series of cases, we are following the lead of numerous observations in the literature. It is striking that these observations should have been reported most accurately at a time when the practice of medicine was more of an art and less dependent on routine laboratory technic. At that time also venesection brought more attention to the veins than is usual at the present time.

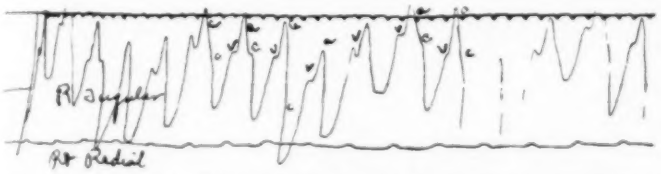


Fig. 4 (Case 2).—Ventricular type of jugular venous pulse; systolic blood pressure 100, diastolic 84; radial rate 100-90, taken just after Figure 3. AV = about 2/5 second. VA = less than 1/5 second.

METHOD

The patient is usually in a semi-Fowler position or flat on his back in bed. The light should be adjusted so as to come from the side. Daylight is preferable to artificial light unless a fairly strong diffuse white light can be obtained. The observer should be seated comfortably on a chair drawn up to the beside. The patient's arm should be held in moderate abduction and supported at the elbow and wrist by allowing it to rest on the palms of the hands. Raising the elbow gradually while flexing the forearm gently back and forth on the arm will soon enable one to find the level of collapse of the veins at any point. The "critical point" of venous collapse is a rough estimate of the venous pressure (method of Gaertner) and thus an index to the relative amount of venous congestion.

19. Pezzi and Gasperini: Arch. mal du cœur **7**:593-608, 1914.
20. Wilson: Nelson's Loose-Leaf Living Medicine **4**:415, 1920.
21. Hill, A. V.: Proc. Phys. Soc., February, 1921; J. Physiol. **54**:332 (March) 1921.

The large branches of the basilic vein seem best fitted for making these observations as they are in an area where the skin is thin, somewhat transparent and usually devoid of much fat or edema. The basilic vein is usually made up of three branches which unite in the region of the median condyle on the ventral or mesial surface of the cubital fossa.

In positive cases the pulsations vary from a mere flicker to large excursions of from 2 to 3 cm., depending on the state of engorgement and the degree of insufficiency. In doubtful cases, if the forearm is kept only slightly flexed so that the surface of the venous level is spread along a centimeter or so of vein, the faint flicker may be more easily detected. Also, if the veins are stripped proximally, by light massage with the finger the pulsations may be more readily identified immediately after each stroke.

Obviously, this method is not applicable to the obese with veins buried in fat, in women with very small veins, in cases with regional edema or in which the veins have been obliterated by thrombi or venous section or obscured by subcutaneous hemorrhage or injections. The pulsations may be magnified by placing a strip of paper or a thread or by observing conveniently placed hairs (the sphygmometer of King).

Tracings of these pulsations are obtained by means of a glass capsule connected with a sensitive polygraph. The capsule should be slightly elongated and shaped to fit the arm over the vein. It is fastened in place by collodion and should not obstruct the course of the pulsations beneath it. The best excursions of the writing pen are obtained by causing the collapsing point of the venous column to fall just beneath the capsule. The registration of these pulsations requires some delicacy of adjustment and much practice, as they have nowhere near the volume nor the force of the jugular pulse. Synchronous radial, jugular or apex tracings are also taken.

In normal individuals and controls, we have been unsuccessful in seeing or obtaining pulsations from the vein in this manner, but occasionally a small sharp systolic wave is obtained from the brachial artery nearby. The collapsing point of the veins was noted, usually with the patient flat on his back if possible, or in relation to the xiphisternum or fifth costochondrial junction (Gaertner) in semi-Fowler position.

Occasionally, the venous pressure was measured by a method slightly modified from that of Hooker [22] or directly with a water manometer by means of a large intravenous needle in the vein. Several tracings of the pulsations were obtained from the manometer during the latter procedure. The usual notations on the size of the heart, murmurs, blood pressure and pulse rate and the changes in response to treatment also were recorded.

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22. Hooker, D. R.: Am. J. Physiol. **35**:73, 1914; ibid. **40**:43 (March) 1916. Hooker, D. R., and Eyster: Bull. Johns Hopkins Hosp. **19**:274, 1908.

Prym (1904), Sewall [16] (1906), Hooker [23] (1914) and others have shown that the venous pressure has a diurnal as well as other physiologic variations for normal subjects, the usual pressure being from 3 to 11 cm. of water. Barach and Marks [24] found that in six heart cases only one varied from the normal. Schott [25] (1912) found that the greater the insufficiency of the myocardium the greater the rise in venous pressure following exercise.

In the majority of our cases, the arterial pressure was low and the volume and tension of the radial pulse poor. The venous pressure, while it tended to be high, especially during the periods of tricuspid insufficiency, varied a great deal during the course of the individual case and seemed to depend on the state of compensation. The normal varied between 6 and 12 cm. of water, with the patient reclining. In marked decompensation with excessive venous congestion and cyanosis, the pressure in two cases rose as high as 22-24 cm. of water but usually was in the neighborhood of 15 cm.

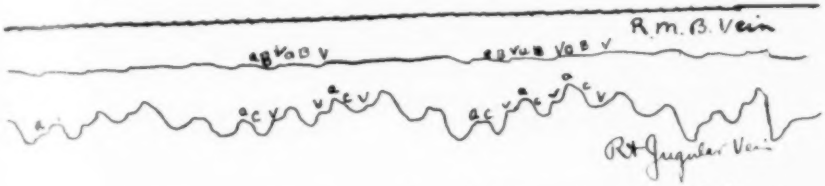

Fig. 5 (Case 2).—Right jugular pulse and right median basilic vein immediately after Figure 4 with less swing to the jugular pens.

EXPERIMENTAL OBSERVATIONS

We have compiled fifty-six cases, mostly within the period between September, 1921, and May, 1922, all showing pulsations in the basilic veins at some period of their stay in the hospital. Many of these cases have been under observation for a long time. When carefully examined, all these cases have shown a certain degree of myocardial damage and most of the signs and symptoms of the tricupsid syndrome: (1) cyanosis and dyspnea; (2) edema and ascites; (3) dilated right heart to percussion, to fluoroscope and to radiocardiogram; (4) a systolic murmur heard best over the lower part of the sternum; (5) a large, pulsating or tender liver; (6) marked pulsations in the jugular veins of the ventricular type and usually showing a split V wave by polygraph; (7) increased venous pressure (12-16 cm. of water); (8) pulsations in the peripheral veins, especially the basilic (both visible and palpable);

23. Hooker (Footnote 22, first reference).
24. Barach, J. H., and Marks, W. L.: Arch. Int. Med. **11**:485 (May) 1913.
25. Schott: Deutsch. Arch. f. klin. Med. **107**:375, 1912.

(9) myocardial damage, shown by electrocardiograms, and occasionally right-sided hypertrophy. The hearts of some eight of these cases have been examined at necropsy. The tricupsid valves in each case have appeared incompetent and the orifice dilated. All the cases have a clinical diagnosis of chronic myocarditis.

The largest group is the arteriosclerotic division in which there are sixteen cases, three of which had hypertrophied prostates. Eleven of these are known to be dead; three have a poor prognosis, and one is unknown. Rheumatic carditis (showing these pulsations) with twelve cases is next. Three of these are subacute. The remainder have mitral stenosis as their chief lesion. Four of the patients are dead and the remainder have a fair prognosis. There are eleven cases of anemia of some type. Seven are dead; two offer a poor and one a fair prognosis, and the state of one is unknown. There are ten cases of a myocarditis on a toxic basis—eight of these are due to hyperplasia of the thyroid (three of which are dead), one to plumbism, and one to obstructive jaundice (dead). The six survivors offer a good prognosis. There are five cases in which syphilis plays the major part—two of the patients are dead and one case in which there is an aneurysm offers a poor prognosis. In the remaining two, the prognosis is only fair. Two other cases offer a good prognosis, one of complete heart block and one of eventration of the diaphragm. Thus, of fifty-six cases there are twenty-eight, or 50 per cent., in which the patients are known to be dead; four offer a poor prognosis, and only eight offer a good prognosis.

PROGNOSIS

In the presence of extensive valvular lesions and marked decompensation, we venture to offer a poor prognosis as the venous pulsations in the veins are usually an indication of pronounced heart failure. In support of this, we have twenty-eight cases in which marked pulsations developed the last few days or weeks before death. All of these cases had a myocarditis and most of them organic valvular lesions as well. Only four cases remain of this group of badly decompensated hearts in which marked venous pulsations were considered an indication for a poor prognosis, and their number is decreasing steadily. Thus thirty-two of fifty cases developing the pulsations presented definitely a very poor prognosis at the time. Of the remainder, the appearance of these pulsations may be considered a warning sign of early heart failure.

The most striking examples are eight cases of marked thyrotoxicosis (from a series of some fifty observed) in which, following suitable treatment of the thyroid, the pulsations disappeared and the patient whose myocardium was not badly damaged completely recovered (five cases). Syphilis, when it is amenable to treatment, falls in the same category. In several patients with decompensated hearts who had shown

pulsations and in whom the pulsations had disappeared under treatment, some extra strain, such as getting out of bed and going to the lavatory, would cause the pulsations to reappear. Along with this the cyanosis and dyspnea increased and a systolic murmur was usually detected where it has been absent just before. Suitable rest then caused the subsidence of symptoms and disappearance of the pulsations in a few hours. Mackenzie states in his chapter on prognosis (p. 348) that "in estimating the value of any abnormal sign or in determining the condition of a heart, the most reliable guide is the manner in which the heart responds to exertion. This again is but an attempt to estimate the amount of reserve force." Usually other clinical signs also warn the clinician of impending danger. The pulsating veins may be, however, the first outstanding sign in the course of the case.

Some twenty-one hospital patients, taken as they came in the wards, and ten normal adults were observed carefully over quite a period of time without showing the pulsations. Only two of these patients had heart disease, and they were well compensated. Acute rheumatic hearts do not show these pulsations as a rule except when they become acutely decompensated. One case followed for four months showed them only twice and then only after the patient got out of bed against orders.

Very often while examining in a routine manner supposed controls, we would find unsuspected signs of early heart failure and the pulsating basilic veins. We have examined within the last three years, since these observations were started, several thousand or so of ambulatory, well compensated clinic patients without having seen the pulsating vein once; yet one or two patients approaching decompensation who show them can usually be found in the clinic or in the ward.

Since the data for these cases was compiled, we have recorded fifty of more cases showing these pulsations.

Observations on the retinal veins suggest that pulsating retinal veins have the same significance as other pulsating peripheral veins.

The following five cases are typical and indicate some of the various conditions in which the pulsations may be found.

REPORT OF CASES

CASE 1.—A. S., a man, aged 46, was under observation from March 1 to May 26, 1921. The clinical diagnosis was chronic carditis, endocarditis, with mitral stenosis and insufficiency, aortic insufficiency, relative tricuspid insufficiency, chronic myocarditis and chronic pericarditis. There was marked decompensation, cyanosis, dyspnea, orthopnea, edema, ascites; marked venous congestion with pulsating jugular and basilic veins and a large, pulsating, tender liver. There was a large overactive, irregular heart, and it was difficult to differentiate the systolic tricuspid murmur from the loud murmurs heard all over the precordia. The blood pressure was 120 systolic, 90 diastolic; the rate was 70-100 and irregular. The patient was receiving digitalis. The venous pulsations were present off and on during the three months the patient was under observation,

and they were very prominent during the last month just before death. They disappeared with improvement or on relief of the congestion by venous section and returned without fail whenever the patient began to feel dyspneic and uncomfortable again with the breaking of compensation.

April 14, 1921, the pulsations in the basilic veins were marked. Venous collapse occurred at the level of the upper border of the clavicle, approximately 22 cm. above the xiphisternum (fifth rib) with the patient in semi-Fowler position. The excursion of the waves at their optimum level was about 2 cm. The venous pressure in the basilic vein with the capsule and mercury surface level with the xiphisternum (fifth rib) averaged 16 mm. of mercury (seventeen determinations). This is equivalent to 20.8 cm. of water. The blood pressure was 117 systolic, 75 diastolic. The radial pulse was 84.

April 19, 1921, the patient was very dyspneic and cyanotic. Venous collapse occurred at 22-23 cm. above the xiphisternum (fifth rib) with the patient in semi-Fowler position. A saline solution manometer was connected to the basilic vein by an intravenous needle. With the vein and surface of the liquid in the manometer level with the manubrium 15 cm. above the xiphisternum (fifth rib), there was a rise of 6.4 cm. in the saline solution column when the connection was made. Therefore, the venous pressure was equivalent to 21.4 cm. of saline solution. Vertical excursions in the manometer column of 0.7 cm. occurred with each heart beat. These were registered by a polygraph (Fig. 2). These tracings lacked the small, sharp brachial artery wave shown in the tracings obtained by the capsule on the skin, and may be considered as the true venous pulsations as they seem to the eye and finger. The blood pressure was 120 systolic, 80 diastolic. The radial pulse was 88.

From May 1 to 26, the decompensation was increasing with occasional relief by venesection. The pulsations were visible at all times except after venesection.

A section was made, May 26, six hours after the patient's death. The heart weighed 800 gm.; there was typical cor bovinum. The right ventricular wall was from 6 to 8 mm. and the left ventricular wall from 10 to 12 mm. thick. The circumference of the valvular rings was as follows: Aortic, 65 mm., mitral 30 mm., pulmonary 85 mm., tricuspic 130 mm. The chorda tendineae were all thickened and those to the mitral leaflets were very broad (1 cm.) and calcareous. The tricuspid valves appeared to be incompetent and the ring relaxed.

The anatomic diagnosis was marked general cardiac hypertrophy and dilatation; chronic mitral and aortic valvulitis with marked stenosis of the mitral valve, less marked of the aortic; fibrosis with calcification of the chorda tendineae to the mitral leaflets with ulceration of the superficial auricular surface and acute thrombus formation; subacute thrombotic endocarditis of both auricles, especially the right; fibrous pericarditis and hydropericardium; general chronic passive congestion; compression atelectasis of the left lung; bronchopneumonia of the right lung. There were multiple areas of fibrosis of the right lung and obliterating pleural adhesions about the mesial surface of the lung on the left; cholelithiasis; fibrous adhesions between the right lobe of the liver and the diaphragm and about the spleen; focal splenic capsular fibrosis; an anemic infarct of the right kidney; slight chronic interstitial nephritis, and multiple erosions of the gastric mucosa.

Case 2.—A man, aged 55, suffered from generalized arteriosclerosis; anginoid attacks; cardiac myomalacia; marked decompensation, with dyspnea cyanosis, orthopnea, edema and ascites; a large, tender, pulsating liver, and marked pulsations in the jugular and basilic veins and of the dorsal veins of the hands. There was a systolic murmur at the xiphisternum and, questionably, a tricuspid murmur. General improvement was noted under treatment with a disappearance of the pulsations in the basilic veins two days before the patient was discharged at his own request.

The patient returned in an ambulance the following night badly decompensated, with marked venous pulsations and a loud systolic, definitely a tricuspid murmur over the xiphisternum. Direct readings with a venous needle showed a venous pressure of 14.3 cm. of saline solution. The collapsing point of the veins was 17 cm. above the junction of the fifth rib with the sternum (patient in semi-Fowler position). The patient developed signs of pulmonary embolism and became markedly dyspneic. Venous engorgement became marked; the blood pressure dropped to 87 systolic, 78 diastolic, while the venous pressure remained somewhat high (15 cm. above the xiphisternum). This was relieved somewhat by venous section. The pulsations though faint were observed until death three days later. The venous pressure continued to drop up to the time of death.

The anatomic diagnosis from a section twelve hours later was: Marked disseminated fibrosis of the entire left ventricle and interventricular septum with complete fibrosis at the apex with pocketing; slight coronary sclerosis without occlusion. There were small mural thrombi in the right ventricle and right auricular appendage; one large and several smaller thrombi in the left ventricle — one small pedunculated thrombus. Terminal septicemia was present; marked hypertrophy of the right ventricle; moderate dilatation of both auricles and the right ventricle, marked in the left ventricle; chronic adhesive pericarditis over the right auricle; petechiae over the base of the left ventricle and on the arch of the aorta; small infarcts on the edge of the left lung;

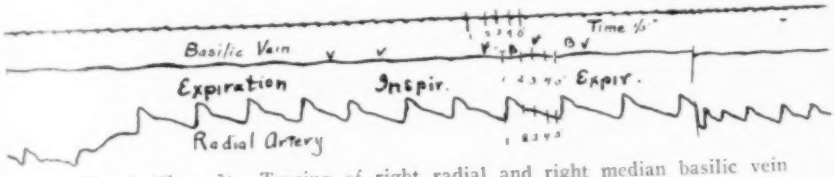

Fig. 6 (Case 3).—Tracing of right radial and right median basilic vein with glass capsule in toxic goiter with fibrillation and moderate decompensation: 1 to 2, *B*, brachial and radial artery systole and just before beginning of regurgitant venous wave — visible pulsation in the pen but not easily registered — a little over one-fifth second in length; 2 to 4, main elevation of *V* wave (almost two-fifths second); 4 to 5, end of wave before next systole (almost one-fifth second) and the usual period for the *A* wave, but as in Case 1, the *A* wave is absent so there is no elevation of the venous pulse similar to that in Case 2 (Figs. 3-5); 3, apex of wave one-fifth second following dicrotic notch (2) and from the beginning of the radial systole, about two-fifths second. It is the venous regurgitant wave or the *V* wave of the jugular pulse.

thrombosis of the large branch of the right pulmonary artery, with large infarcts in the upper and lower lobes of the right lung. There were pneumonic consolidation above the infarct in the lower lobe of the right lung; a light acute fibrinous pleurisy over the infarct in the right lung; a slight pleural effusion, more marked on right; a moderate acute splenic pulp reaction; a moderate chronic diffuse nephritis with a retention cyst in the left kidney; chronic passive congestion of the viscera, and cloudy swelling of the viscera.

The circumferences of the valve orifices were: Aortic 80 mm., mitral 95 mm., pulmonic 75 mm., and tricuspid 140 mm. The tricuspid orifice seemed dilated and the valves incompetent.

Case 3.—A man, aged 48, was under observation with a clinical diagnosis of toxic hyperplasia of the thyroid with toxic myocarditis and auricular fibrillation. The basal metabolism was 84 + per cent. There were marked dyspnea and cyanosis; an enlarged overactive heart, and slight edema of the extremities. The liver was pulsating and slightly enlarged. The jugular and

basilic veins were pulsating markedly. The excursion of the pulsation in the basilic veins was from 2 to 3 cm. A systolic murmur was heard over the xiphoid, and a diagnosis of relative insufficiency of the tricuspid was made. No valvular lesions were present. The systolic blood pressure was 130, the diastolic 80. The pulse rate was 130-100 and irregular.

Polygraph tracings of the jugular vein showed a large undulating jugular wave with an absent A wave, a small C wave and a broad plateau type of V wave almost one-fifth second in duration. The liver tracings (Fig. 7) showed a large wave of ventricular type with a prominent and occasionally split V wave. The basilic vein tracings (Fig. 6) showed only one large undulating wave, late systolic in time, and following the dicrotic notch of the radial pulse. The pen lever registered a small systolic pulsation synchronous with, and starting just an instant before, the radial lever beat. This pulsation was due to the brachial artery nearby and was too faint to show up well on the tracings (Fig. 6, *B*).

Within two weeks following the instillation of radium emanation needles into the thyroid, the pulsations disappeared following the gradual subsidence of all the symptoms relative to myocardial weakness and tricuspid insufficiency. The heart was supported by quinidin and the usual treatment. Six months later, the patient had gained 50 pounds (22.7 kg.) and showed no abnormal symptoms.

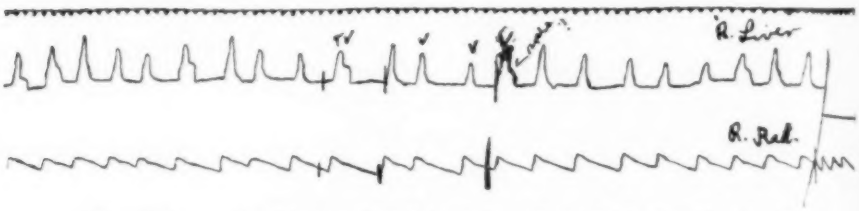

Fig. 7 (Case 3).—Liver and radial tracing taken right after the tracing in Figure 6, showing ventricular type of liver tracing with an occasional split *V* wave somewhat similar to the split *V* wave in the jugular tracings.

Case 4.—B., a man, aged 34, suffered from combined system disease which was of interest because the venous pulsations led to the early diagnosis of dilatation and failure of the heart in a very spectacular manner.

The lower extremities and sphincters were paralyzed. There was myocarditis of a low grade in keeping with the general weakness and debility. The heart was regular and showed no valvular disease, and seemed able to keep up a good circulation. The patient was being used as a control, showing no evidence of failure, no tricuspid murmur, venous congestion or pulsations in the peripheral veins. Catheterization of about 2 liters of urine brought about an attack of acute syncope. This was followed almost immediately by a period of marked paroxysmal tachycardia (rate, 140-200) for about thirty-six hours. Approximately one hour after the onset of the tachycardia, large pulsations were noted in the basilic veins. A short time later, the liver was found to be tender and pulsating. Edema of the ankles developed rapidly. There was marked cyanosis and dyspnea. The collapsing point of the median basilic veins was 14 cm. above the xiphisternum with the patient in a semi-Fowler position. When the pulse rate was slowed down by vagal stimulation, a faint systolic murmur could be heard over the tricuspid area one hour after onset of tachycardia. The right heart was enlarged to percussion. By the next day the pulse rate had dropped to 80. The blood pressure during this time had been 80 systolic, 60 diastolic. The venous pulsations continued over the whole month following the attack up to the last twenty-four hours just

before death, when the venous pressure fell remarkably and the pulsations were no longer visible. The tricuspid murmur, cyanosis and dyspnea, edema and tender liver also persisted. The venous pressure varied considerably—at first it was quite high. The collapsing point was level with the second rib when the patient was in semi-Fowler position, or approximately 15 cm. above the xiphisternum. Following the attack of syncope, it dropped quite markedly (from 5 to 10 cm.) and varied from time to time. The pulsations also varied in the prominence and amount of excursion. With a high venous pressure they were generally pronounced and vice versa. No necropsy was permitted.

CASE 5.—A man, aged 45, had a history of rheumatic fever. The clinical diagnosis was chronic myocarditis and endocarditis with mitral and tricuspid stenosis and insufficiency; auricular fibrillation and decompensation with marked anasarca.

April 4, 1922, the heart was dilated to the right and the left with a coarse vibratory systolic murmur loudest over the end of the sternum and merging with a systolic murmur over the apex of different quality and intensity. There was a large, nontender, pulsating liver and marked pulsation of the veins over the forehead, arms, hands and feet was noted. Pulsations were systolic or presystolic in time over the veins and the liver. There was a marked bounding pulsation in the jugular veins, the right jugular bulb especially standing out prominently about 2 cm. in diameter, in the right supraclavicular space. The systolic blood pressure ranged from 120 to 100; the diastolic was 78. The pulse was 50-110. A polygraph tracing of the jugular vein showed an absent A wave and a high split plateau type of V wave. The venous pressure was approximately 14 cm. above the xiphisternum with the patient in a semi-Fowler position. Pulsations could not be recorded from the other veins as the polygraph was out of order.

Under digitalization and later quinidin the decompensation improved and the venous pressure and pulsations diminished, but these were still present on discharge three weeks later.

COMMENT

The tricuspid syndrome has been discussed by many authors, usually with entire agreement as to what actually composes a relative insufficiency of the tricuspid valve, so that we shall not review it here. Its signs and symptoms are briefly enumerated above. The common occurrence of relative insufficiency is also well recognized. Leube [26] (1905) says, "Das eine funktionelle Trikuspidalinsuffizanz in Verlaufe der Anämie auftreten kann, ist selbst verst ändlich." G. Canby Robinson [27] (1920) writes that "an increase in pressure within the right ventricle sufficient to produce tricuspid incompetence may be caused by asphyxia or even by prolonged holding of the breath, or by severe exertion. Lesions such as emphysema or fibrosis of the lungs, ... nutritional disturbances in the cardiac muscle, such as occur in severe anemia, in fever, or with a diminished blood supply to the myocardium resulting from obstruction in the coronary arteries" give rise to incompetence. Our series of cases presents all of these factors.

Mackenzie [1] states that "although actual disease of the valves is rare, incompetence of the tricuspid orifice is extremely common, so common,

26. Leube: Ztschr. f. klin. Med. **57**:199-207, 1905.
27. Robinson, G. C.: Nelson's Loose-Leaf Living Medicine **4**:376, 1920.

indeed, that I am inclined to look upon the valves as being barely able to close the orifice perfectly. . . . Experimentally, it has been found impossible to raise the pressure in the right ventricle, on account of the ease with which regurgitation takes place through the tricuspid orifice." He has noted the frequent occurrence of a "greatly widened orifice (tricuspid) postmortem, while during life there was no systolic murmur." This seems to be the usual experience of most pathologists, in fact, the dilatation of the tricuspid ring and incompetency of its valves is looked on with complacency and even regarded as "normal" at postmortem.

We wish to emphasize, therefore, a certain element in myocardial disease which plays the great part in causing the pulsations in the veins, and that is the weakness of the tricuspid orifice. King [6] (1837) and Gibson [28] (1880) thought that this weakness served a safety valve function in relieving the overburdened ventricle.

The pressure on the right side of the heart is low and the musculature thin and any increase in pressure or stasis from weakness, etc., may cause dilatation very readily because of the thin and flabby tissues involved. Myocardial weakness is the fundamental factor for the onset of decompensation and the occurrence of dilatation.

Benson [5] in 1836 contended that the pulsations in the peripheral veins were due to the propagation of a regurgitant impulse from the right ventricle through the auriculoventricular orifice into and throughout the distended veins, no matter how incompetent their valves.

We think it can really and conclusively be demonstrated in several ways that these pulsations are centrifugal, associated with venous stasis and propagated from the right ventricle when that chamber contracts:

First, if the basilic vein is just obliterated several centimeters proximal to its branches, by very light pressure made with the thumb of the hand supporting the patient's arm at the elbow, the pulsations can be made to disappear and reappear at will. It will be noted on close observation at these times that the pulsations are distinctly centrifugal. They do not occur in the distal veins while the veins fill up during the period of compression of the basilic vein.

Second, if the forearm is held perpendicularly and the basilic vein is again lightly compressed, during the rise of the venous level due to the blood flowing into the veins from the capillaries there is no observable pulsation (the explanation suggested by Gaertner among others). If the level of compression on the basilic vein is now raised above the "critical point" of collapse, the pulsations will be seen proximal to the point of compression and not distal to it. A similar maneuver

28. Gibson: Edinburgh M. J. **25**:979, 1880.

has been used on the jugular vein by many authors to demonstrate tricuspid insufficiency.

Third, if pressure is made on the midportion of the veins and the proximal portion is stripped toward the heart, the pulsations return and mount higher and higher peripherally in waves synchronous with the heart beat to the critical level or to the compression point.

It has often been observed that pressure on the liver will make the pulsations in the jugular veins more prominent. We have found that firm pressure on the liver will raise the collapsing point in the basilic vein several centimeters (from 6 to 10 cm.), depending on the degree of pressure. This gradually declines in from five to ten seconds, as the heart and vessels compensate for the increased congestion even though the pressure is continued. The respiratory variations are seen to occur as stated by Gaertner and others. We have been unable to observe these pulsations in several experiments on ourselves following the relaxation of the capillaries by heat.

Reference has been made in the literature to pulsations seen in the veins of the arm, forearm and hand, the femoral or crural veins, the veins of the lower leg and foot, varicose veins of the leg, the veins of the thorax and abdomen, the forehead, temples and scalp, the retina and the thyroid. Of course, the jugular veins throughout their course have received much study and the interpretation of their pulsations has given rise to a tremendous literature. Pulsations elsewhere than in the neck and basilic veins, veins of the hand and the retinal vessels seem to be uncommon in our experience, except in cases of marked decompensation with pronounced regurgitation and engorgement. In all such cases the prognosis was very bad as the patients died soon after. In this they resembled the cases reported in the literature. In our cases, as noted by the early workers, venous section caused the pulsations to disappear because congestion was relieved.

Mackenzie [29] (p. 25) warns us that "it must be borne in mind that between the right ventricle and the jugular vein there is interposed a dilating auricle and a capacious superior vena cava and that a wave can only appear in the jugular after the auricle and vena cava have been overfilled." It would appear that a small volume of blood regurgitated into the congested vena cava would not make much difference in the pulsations on the surface of a large vein like the jugular vein. In the case of a small vein, however, in the presence of congestive failure, this would have a more evident influence on the excursions of its surface because of the relatively greater volume changes per caliber. In the very small veins the walls become less flaccid as the caliber decreases, so that the variations in surface level may be present although they are not

29. Mackenzie: Am. J. Med. Sc. **134**:12, 1907.

visible. This is also true when the vein walls are sclerotic, as is often the case of the dorsal veins of the hands in elderly people.

Anatomically, the liver, the neck and axillary veins are so situated as to receive directly the regurgitant wave coming from the right ventricle through a dilated right auricle into the vena cava. The liver can readily absorb small pulsations because of its structure, and they may not be noted. The jugular vein, because of its height above the heart, is not affected so much by a relatively small increase in venous pressure and congestion, and because of its large size it readily absorbs small changes from regurgitation which may escape observation. These may be detected, however, by such changes as splitting of the V wave in the polygraph tracings.[30]

Gaertner suggested that in the manner of a manometer the arm veins would show the venous pressure, and that this could be considered as equal to the auricular pressure. These veins are of relatively good caliber and their connections with the engorged vena cava and right auricle are quite simple and direct. If congestion occurs with the consequent elevation of the venous pressure, dilatation not only of the auriculoventricular ring becomes possible but also dilatation of the much more elastic veins is readily demonstrable in the periphery. Benson's argument that a pulsation can readily travel up a vein already distended by congestion without interference by its valves seems well taken. It is very likely, furthermore, that as the congestion (and the venous pressure) becomes greater, the venous valves both of the jugular bulb and further in the periphery become incompetent and the regurgitant waves can progress distally in greater volume. This seems borne out by the variation in size of the venous pulsations in proportion to the changes in venous pressure and congestion. It is only logical, therefore, to suppose that a regurgitation of only a small amount of blood from the right ventricle would cause visible oscillations of some magnitude in these veins. It is for these reasons and on our experimental observations that we base our contention that pulsations in the basilic veins are early associated with venous stasis and tricuspid insufficiency.[31]

30. Mackenzie (Footnote 28). Lewis: Clinical Disorders of the Heart Beat, Ed. 5, Shaw and Sons, 1920.

31. Since these observations have been made, two unusual cases have presented some interesting pulsations. A patient with marked organic tricuspid stenosis and insufficiency, proved by necropsy, showed marked presystolic and systolic pulsations in the liver, jugular veins and vessels of the arm, hand and retinal veins. Another patient with complete heart block showed pulsations in the basilic vein with the contraction of the auricle and superimposed pulsations following the contraction of the ventricles. There were long periods of asystole of the ventricles with well marked peripheral vein pulsations associated with contraction of the auricles. Attacks of ventricular tachycardia also were observed with pulsations of the veins following contractions of the auricles and ventricles superimposed.

It seems that the prophecy made by King in 1837 is being verified. He said:

> I may venture to express an anticipation that more careful observation, even with the unassisted eye, will detect pulsating veins more frequently than has hitherto been done, and even render this fact available in diagnosis. I would also hope that the examination of the veins by the help of the sphygmometer may become still more generally serviceable in practical matters.

SUMMARY

The literature contains many isolated references to venous pulsations in the peripheral veins, most of which were published many years ago. The significance of these pulsations has not been generally recognized. It is our opinion, based on careful study of over fifty-six cases showing these pulsations, that they are present only during congestive failure and relative incompetency of the tricuspid valve. These observations have been checked up on several thousand clinic and ward patients seen within the last three years and fifty more cases noted with tricupsid syndrome and pulsations in the basilic veins. Their presence in a large variety of ward cases suggests that they are of value in making an early diagnosis of myocardial weakness or failure with passive congestion and relative tricuspid insufficiency in cases in which these factors would ordinarily be overlooked. Their magnitude seems to be an indication of the degree of incompetency of the tricuspid valve and also of the heart musculature. In cases of markedly damaged myocardium, their presence is thought to offer a bad prognosis, as twenty-eight out of thirty-two such patients have died within a year after observation. Cases featuring hyperthyroidism, arteriosclerosis, anemia, mitral stenosis and syphilis are the most common in presenting these pulsations.

The peripheral pulsations are more prominent and more frequently observed in the basilic veins of the arm and forearm. Their pulsations follow the brachial systole. This retardation of the regurgitant stasis waves seems to be due to the relaxed and engorged state of the veins and a decreased velocity in a low pressure system, and is similar to the A, C and V waves of the jugular pulse. The congestion allows the propagation of the impulse even though the valves may be competent.

CONCLUSION

Pulsations in the peripheral veins and especially in the basilic veins of the arms are suggested as an early and valuable sign in detecting the presence of myocardial or congestive heart failure together with a relative tricuspid insufficiency. Their magnitude interprets the degree of myocardial and tricuspid incompetency. Their appearance in cases of marked decompensation suggests a bad prognosis.

THE EFFECT OF CHANGES IN POSITION OF THE HEART ON THE Q-R-S COMPLEX OF THE ELECTROCARDIOGRAM *

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That the position of the heart in the chest has an influence on the shape of the electrocardiogram as taken by the usual three leads was pointed out in the early work from Einthoven's laboratory.[1] The modifications appearing on rotation of the body from side to side, on changes from the recumbent to the erect position, and in the phases of respiration have all been attributed to this factor. Dextrocardia offers one of the greatest possible variations in cardiac position and here, as is well known, the electrocardiogram is reversed. Stout subjects with transversely placed hearts usually give electrocardiograms with R_3 of least amplitude while slender subjects with pendulous hearts usually show the least amplitude in R_1. Lateral displacements of the heart due to pleural effusions, air or adhesions also are known to modify the electrocardiogram. According to Pardee,[2] such displacements to the right reduce the height of R and bring Q into prominence. Movement of the heart to the left, on the contrary, changes the curves but little.

In man experimental procedures designed to alter the heart-thorax relationships other than those mentioned have been obviously impossible. Several workers have, however, varied the position of the leads so that there was at least a clever imitation of a change in the heart position. Herrmann and Wilson [3] substituted Leads II and III for Leads I and II and inverted Lead I. By repeating this process they practically rotated the heart in stages of 60 degrees each. Counterclockwise rotation gave curves resembling left sided ventricular preponderance, while clockwise rotation gave curves resembling right sided preponderance. Cohn [4] rotated his leads around a triangle laid out as large as possible on the chest. This simulated the rotation of the heart on its anteroposterior axis. Many of the pictures secured resembled preponderance

* From the Physiological Laboratory of the University of Wisconsin Medical School.

1. Einthoven, Fahr and de Waart: Arch. f. d. ges. Physiol. **150**:275, 1913.
2. Pardee: Clinical Aspects of the Electrocardiogram, New York, Paul B. Hoeber, 1924, p. 45.
3. Herrmann, G. R., and Wilson, F. N.: Heart **9**:91 (April) 1922.
4. Cohn: Heart **9**:311, 1922.

curves at least so far as the Q-R-S complex was concerned. The T waves, however, were always in the same direction as the main deflection.

All the authors mentioned above have agreed that the position of the heart in the thorax might greatly influence the electrocardiogram and that at times this might be far reaching. For example, in the case of a left ventricular preponderance, the condition as shown by the curves might be estimated as marked, slight, or even absent according to whether the heart was in a transverse or pendulous position. It is thus readily seen that an accurate analysis of the effects of cardiac position on the electrocardiogram would be of value not only in interpreting variations in normal records but in evaluating abnormal curves.

Animal experimentation has not been used to any extent in this problem owing to the general feeling that manipulation with the chest open made it impossible to secure electrocardiograms sufficiently normal to be of value. So far as we can find the only paper dealing with the problem in animals is that of Boden and Neukirch,[5] who led off from a vessel of saline solution in which an isolated perfused heart was placed. With such a device the heart could be placed in any position desired relative to the leads. They found that rotation of the isolated human or animal heart around its longitudinal axis to the right gave a left sided effect, while rotation in the opposite direction gave curves resembling right sided preponderance. Their experiments, being made under such highly artificial conditions, have not seemed very convincing to other workers.[3]

In the work here reported we have secured rotation of the heart around its anterior-posterior and longitudinal axes. Dogs under morphin-ether anesthesia were used in all experiments. In the first series of experiments, a rib was resected and ligatures were tied around the pericardium just below the apex of the heart. The attachments of the pericardium to the diaphragm were broken up, and one ligature was carried by a needle through each lateral wall of the thorax. By pulling on these ligatures the apex of the heart could be brought in contact with either side of the thorax, the heart thus describing an arc of about 60 degrees on its anterior-posterior axis. The opening in the chest was closed and the animal resumed its own respiration. Electrocardiograms were then made with the heart in various degrees of rotation.

In later experiments the chest was split in the midline and the animal kept throughout under artificial respiration. The more complete exposure afforded in these cases allowed us, by the use of small fish hooks inserted either into the pericardium or through the pericardium

5. Boden and Neukirch: Arch. f. d. ges. Physiol. **171**:146, 1918.

into the epicardium, to rotate the heart on its longitudinal axis. Ligatures placed as before brought about rotation from side to side. The heart was anchored at its base by two ligatures sewed into the fascia around the aorta and fastened to the thoracic walls.

The majority of our records were made by taking simultaneously with two Edelmann galvanometers, first Leads I and II and then Leads II and III. In a few recent experiments we have added a third galvanom-

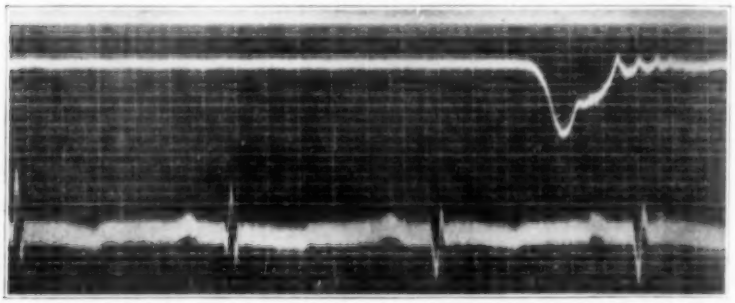

Fig. 1.—Increase of Q wave and disappearance of S wave in Lead I on pulling the heart to the right.

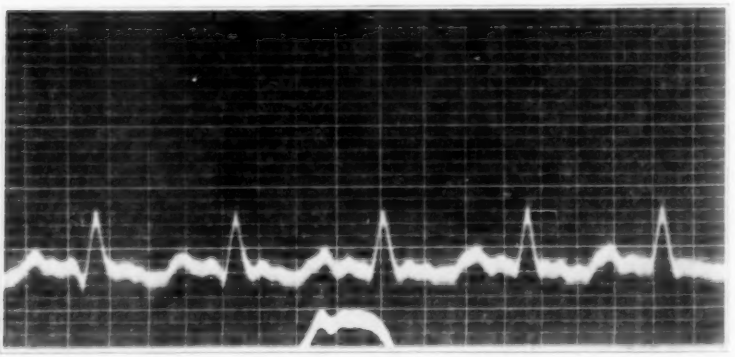

Fig. 2.—Disappearance of the Q wave in Lead I on pulling the heart to the left.

eter and taken all three leads simultaneously. Throughout our work we have accepted the validity of the Einthoven triangle, and have used his formula in determining all electrical angles. Our standard has been that R_1 and R_3 should approximately equal R_2. We have allowed one-tenth millivolt variation in these measurements, since it was impossible under the conditions of our experiments exactly to reproduce the same degree of rotation for each set of records. This variation if attributed entirely either to R_1 or R_3 would produce a variation of not

more than 5 degrees in the electrical angles. This necessary error in technic is not large enough to interfere with a determination of the general effect of a given rotation. In those cases in which R_1 and R_3 failed to equal R_2 by more than a millimeter the records have still been found valuable. By using, first, the formula of Einthoven which determines the electrical angle from R_2 and R_3 and, second, the formula involving R_2 and R_3, the greatest variations in the electrical angle which are possible from the given data are found. If these point in the same direction, the experiment is of course satisfactory and indicates the qualitative effect of the rotation. Since phase differences might lead to uncertain calculations, R_2 has always been used as the standard for measurements. R_2 and R_3 are usually synchonous, the variations in synchrony being found most often between R_1 and R_3.

In those experiments in which the chest was opened, ligatures applied and the thorax closed, the electrocardiograms were usually indistinguishable from controls taken before the operation. Electrocardiograms from animals with an open chest are also usually normal. By this we mean that the waves are all apparent and of the usual form. Only two variations are common. R_3 is often notched and the T wave is apt to be negative or diphasic, a condition which may appear in the dog under almost any operative procedure.

ROTATION AROUND THE ANTERIOR-POSTERIOR AXIS TO THE RIGHT

The axis for rotation around the anterior-posterior axis to the right was where the base of the heart crossed the midlongitudinal line. This point was chosen because it was here that the heart was anchored by ligatures. A line was drawn from this point to the apex of the heart. The angle between this line and the horizontal has been termed the anatomic angle. This anatomic angle as determined in the open chest was ordinarily about 80 degrees. When pulled to the right it was increased to approximately 110 degrees, and when pulled to the left it was reduced to about 60 degrees. According to the simple application of Einthoven's triangle, when the heart is pulled this distance to the right one would expect a decreased or inverted R_1, a decreased R_2 and an increased R_3. An analysis of our results, however, shows that R_3 in twenty-nine experiments increased in only 76 per cent. of the cases; R_2 decreased in only 31 per cent. and R_1 decreased in only 45 per cent. From this it is evident that the electrical axis did not regularly vary with the anatomic, and that in some cases it increased and in others decreased. It varied in direction inversely with the increase or decrease in size of R_1.

In Table 1 data are presented illustrating these conditions in six experiments. The other twenty-three experiments showed similar variations.

The most consistent change in these curves concerned the Q wave. In sixteen of the twenty-nine cases, the descent of the Q increased in Lead I with rotation to the right. In ten others Q appeared after being absent in the normal. In three cases Q was absent or remained the same under both conditions. It is to be recalled that Q is seldom if ever found in Lead I in right sided preponderance but that it may appear in Lead III. Yet in our attempts to imitate right sided preponderance by rotation to the right around the anterior-posterior axis, the Q wave either appeared or increased in Lead I in all but three of twenty-nine cases. Figure 1 gives an illustration of such a change in the Q wave. In Lead II the Q wave appeared in 80 per cent. of the curves, an increase of 28 per cent. over the normal, while in Lead III the Q wave was found in only 34 per cent. of all records, a decrease of 11 per cent. from normal. This indicates that we were not very

TABLE 1.—*Effect of Rotating the Heart to the Right Around Its Anterior-Posterior Axis*

	Experiment	Anatomic Axis, Degrees	Electrical Axis, Degrees	R_1	R_2	R_3
Normal	6	83	67	7.0	20.0	12.0
Pulled right	"	110	63	12.0	27.3	15.0
Normal	18	80	83	1.0	8.5	7.4
Pulled right	"	108	14	4.0	3.0	—1.2
Normal	8	78	70	8.0	23.0	15.0
Pulled right	"	98	75	7.0	27.0	20.0
Normal	16	93	68	5.0	15.9	10.0
Pulled right	"	115	86	1.25	19.5	18.0
Normal	10	74	71	4.0	12.0	8.0
Pulled right	"	113	65	4.0	10.0	5.8
Normal	4	72	81	0.5	12.0	10.0
Pulled right	"	109	109	—2.0	4.0	6.0

closely imitating right sided hypertrophy. These results are, however, in line with what Boden and Neukirch found on rotation to the right around the longitudinal axis.

On rotation to the right around the anterior-posterior axis, the S wave behaved in a manner exactly opposite that of the Q wave, and therefore opposite to what should be expected were we imitating right sided preponderance. When the heart was pulled to the right, the S wave disappeared in Lead I in seven cases in which it had been present normally; increased in only one, and appeared anew in only one. Figure 1 illustrates such a disappearance of the S wave. Yet it is to be remembered that right sided preponderance is characterized by a large S in Lead I. S in Lead III was present in all cases after right sided rotation, having increased or appeared anew in four experiments. In right sided preponderance S_3 is, of course, small or abstract.

It was evident from the foregoing data that merely pulling the heart to the right did not give the picture expected on theoretical grounds, nor did it resemble right sided preponderance to any great degree.

ROTATION AROUND THE ANTERIOR-POSTERIOR AXIS TO THE LEFT

The axis for rotation around the anterior-posterior axis to the left was the same as for the right, the heart being pulled to the left until the apex touched the chest wall, decreasing the anatomic angle to about 60 degrees. According to the principle of Einthoven's triangle, one should expect such a rotation to the left to give an increased R_1, a variable or increased R_2, and a small or inverted R_3. Our results show that R_1 increased in 63 per cent. of thirty experiments; R_2 decreased in

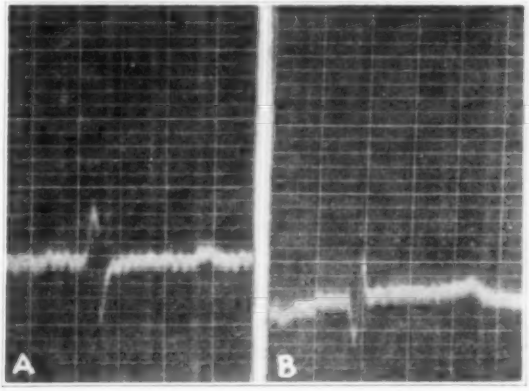

Fig. 3.—Appearance of the Q wave and the disappearance of the S wave in Lead III on pulling the heart to the left; *A*, before, and *B*, after heart is pulled to the left.

60 per cent., and R_3 decreased in 80 per cent. This is a much closer approximation to the theoretical than is secured on rotation to the right, and the electrical angle is accordingly reduced in the majority of these experiments; in some of them it follows the anatomic axis rather closely. Many of the curves very definitely resemble left sided preponderance. The exceptions, however, are sufficiently numerous to indicate that, as before, some other factor was operating in these rotations. Table 2 shows data from six experiments in which the heart was rotated to the left. The other experiments showed similar variations and are therefore not tabulated.

On rotation to the left the occurrence of the Q wave is reduced from 62 per cent. in Lead I to 15 per cent., while in Lead III it increases from 45 to 68 per cent. Figures 2 and 3 illustrate these conditions.

This is, of course, exactly the opposite to what is found in left sided preponderance, in which condition Q may be found in Lead I but is rarely if ever found in Lead III.

The S wave again shows a direction of change opposite to that of Q in all leads. It appears less often in Lead III than in the normal, but more often in Lead I. The percentage of change, however, is not so large. This again is exactly the opposite to the average results for left sided preponderance. Figure 4 illustrates the appearance of S in Lead I.

ROTATION AROUND THE ANTERIOR-POSTERIOR AXIS TO THE RIGHT WITH COUNTERROTATION AROUND THE LONGITUDINAL AXIS TO THE LEFT

The results so far presented show that rotation around the antero-posterior axis neither consistently fulfils the requirements of Einthoven's

TABLE 2.—*Effects of Rotating the Heart to the Left Around Its Anterior-Posterior Axis*

	Experiment	Anatomic Axis, Degrees	Electrical Axis, Degrees	R_1	R_2	R_3
Normal	11	76	80	2.7	11.5	9.0
Pulled left	"	51	82	1.6	11.7	10.0
Normal	10	74	71	4.0	12.0	8.0
Pulled left	"	48	49	10.0	15.0	5.0
Normal	15	85	77	5.8	27.5	21.1
Pulled left	"	72	68	9.5	28.2	17.7
Normal	12	77	57	6.5	13.0	6.0
Pulled left	"	64	40	10.5	13.0	2.0
Normal	27	83	60	4.2	8.3	4.2
Pulled left	"	52	83	1.0	8.3	7.2
Normal	22	77	65	5.3	12.0	6.9
Pulled left	"	67	43	7.0	9.0	2.2

triangle nor duplicates the usual results found in ventricular preponderance. It was obvious that another factor was involved. This we found to be rotation around the longitudinal axis of the heart, it being impossible to displace the heart to either side without such rotation. An anatomic examination showed that our right displacements involved a rotation around the longitudinal axis of about 24 degrees. Displacement to the left occasioned a longitudinal rotation of about 17 degrees. It seemed that the smaller degree of rotation in this direction might account for the closer approximation to the theoretical.

We next ran a series of experiments in which the heart was first displaced to the right and then counterrotated on the longitudinal axis to the left in the hopes of compensating for the rotation around the longitudinal axis involved in the displacement. Data from six such experiments are presented in Table 3. It will be noted that, regardless of whether the electrical angle increased or decreased on mere displacement,

it consistently increased above normal on the counterrotation. This never failed in twelve experiments. Although in all these cases on counterrotation the electrical axis approached the anatomic it equaled it in only one case. This was due to two reasons, one being that what we have called the anatomic axis is a line from the point of rotation to the cardiac apex. It is from 10 to 15 per cent. steeper than the axis described by Cohn.[4] The other is that the exact extent of counterrotation necessary could of course not be determined at the time of experiment but had to be estimated at necropsy.

TABLE 3.—*Effects of Rotation to the Right Around the Anterior-Posterior Axis Followed by Counterrotation to the Left Around the Longitudinal Axis*

	Experiment	Anatomic Axis, Degrees	Electrical Axis, Degrees	R_1	R_2	R_3
Normal	27	83	67	3	6.5	4
Pulled right	..	120	53	6	9	3.5
Counterrotated left	..	120	93	0	7.5	8
Normal	24	84	63	8.9	20	10.9
Pulled right	..	112	72	5.5	17	11.8
Counterrotated left	..	112	{83 {85	2.2	{16 {12	10.9
Normal	28	82	51	7.3	11.1	4
Pulled right	..	108	74	3.2	11.1	8
Counterrotated left	..	108	90	0	10	10
Normal	21	80	67	6.4	17.3	10.5
Pulled right	..	110	97	—1.1	12.7	14.7
Counterrotated left	..	110	113	—2.2	10	13.1
Normal	33	80	84	2.0	12.6	11.1
Pulled right	..	106	64	5.0	14.7	8.3
Counterrotated left	..	106	86	1.5	8.4	7.8
Normal	31	80	68	5.0	2.0	0.0
Pulled right	..	115	81	19.0	18.0	18.0
		115	87	12.0	15.0	17.0

In all these experiments R_1 decreased and R_3 increased relative to R_2. This of course is necessary if an increase is to be found in the electrical angle. Curves illustrating this point may be seen in Figure 5, *A*. As compared with the curves obtained from displacement to the right, on counterrotation the Q wave in Lead I disappeared in 27 per cent. of the cases and decreased in 50 per cent. In Lead III the Q wave, however, increased to 80 per cent. of all cases. The S wave was only occasionally present in Lead I but was found in all cases in Lead III. From this description it is evident that cardiac displacement to the right with counterrotation on the longitudinal axis to the left gives definite signs of right sided preponderance. These are to be seen in the R and Q waves. The S wave does not follow the rule for right sided preponderance.

ROTATION AROUND THE ANTEROPOSTERIOR AXIS TO THE LEFT WITH COUNTERROTATION AROUND THE LONGITUDINAL AXIS TO THE RIGHT

In twelve experiments, with two exceptions, the electrical angle was greatly decreased on counterrotation, regardless of the direction of the change on mere displacement to the left. The two exceptions may well have been examples of overcompensation. Table 4 gives the data from five of these records. R_1 is always increased and R_3 decreased in relation to R_2. In addition R_2 itself always showed a decrease on counterrotation. On counterrotation the Q wave in Lead I increased in occurrence from 15 per cent. in the simple displacement curves up to 70 per cent. In Lead III it decreased from 68 to 30 per cent. The S

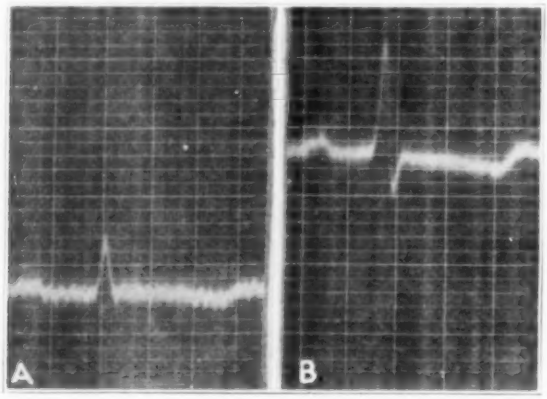

Fig. 4.—Appearance of S wave in Lead I on pulling the heart to the left; *A*, before, and *B*, after the heart is pulled to the left.

wave was present in all cases in Lead III after counterrotation, and in the majority of cases it was considerably deepened.

From the foregoing it will be seen that displacement to the left with counterrotation gives a picture practically identical with left sided preponderance. Many of the curves are very characteristic indeed, as may be seen in Figure 5, *B*.

HEART HELD IN ITS NORMAL POSITION AND ROTATED AROUND ITS LONGITUDINAL AXIS TO RIGHT AND LEFT

From the preceding experiments it seemed evident that right and left sided displacements around the anterior-posterior axis did not give the expected results owing to the simultaneous rotation which necessarily occurred around the longitudinal axis. This point was definitely proved

by holding the heart in its normal position and rotating either to the right or left around the longitudinal axis. In Table 5 may be seen the result of such rotations.

In all cases tried with rotation to the right, the electrical angle was remarkably decreased, several times becoming negative, this being due to increases in R_1 and decreases in R_3. The Q wave in Lead I, increased both in incidence and size, was present in all cases on rotation. It was invariably absent in Lead III. The S wave decreased in Lead I, but was found in all cases in Lead III. These are typical signs of left sided preponderance. Curves illustrating rotation to the right may be seen in Figure 5, *C*.

In Table 5 are also presented the data for rotation to the left. In all cases the electrical angle was increased owing to a smaller R_1 and

TABLE 4.—*Effects of Rotating to the Left Around the Anterior-Posterior Axis Followed by Counterrotation Around the Longitudinal Axis to the Right*

	Experiment	Anatomic Axis, Degrees	Electrical Axis, Degrees	R_1	R_2	R_3
Normal	23	86	46	8.7	12	3.5
Pulled left	..	67	30	10	10	0
Counterrotated right	..	67	22	6.9	6	−1
Normal	25	78	69	2.5	9	5.8
Pulled left	..	61	(45)65	5.8	(8)7	....
Counterrotated right	..	61	(−14) −5	10.8	3	−4.1
Normal	28	82	51	6	9.4	4
Pulled left	..	64	59	4	7.8	4.5
Counterrotated right	..	64	13	8	5.6	−2
Normal	30	82	57	9.1	16.2	7.5
Pulled left	..	67	54	7.7	13.7	5.6
Counterrotated right	..	67	30	10	9.4	0
Normal	22	77	65	5.2	12.0	6.9
Pulled left	..	67	43	7.0	9.0	2.2
Counterrotated right	..	67	30	7.0	8.0	0.0

a larger R_3. Q decreased very markedly both in size and incidence in Lead I but increased also markedly in Lead III. The S wave on the contrary increased in Lead I and decreased in Lead III. These are the signs of right sided preponderance. Curves illustrating rotation to the left may be seen in Figure 5, *D*.

COMMENT

Our results do not seem to agree with Einthoven's explanation for the rather frequent exaggeration of S in Lead I when the subject turns on his right side. Einthoven [1] suggested that the appearance of this wave was due to the projection of a sagittal potential on the frontal plane due to a rotation around the longitudinal axis. One would expect such a rotation to occur from left to right, but experimentally this rotation has always given us an enlarged Q and a reduced or absent S in Lead I.

Herrmann and Wilson's [3] conclusion that there is no definite relation between the form of the ventricular complex and the relative weight of the two ventricles unless there is a marked hypertrophy receives both justification and explanation by our findings. Within certain limits the signs of ventricular preponderance may be accentuated, neutralized or reversed by varying the position of the heart, particularly the degree of rotation around the longitudinal axis. These effects are, of course, most marked when the signs of preponderance are least marked, that is, in cases of slight hypertrophy. When the heart is greatly hypertrophied, no change in position is sufficient to obscure the true picture.

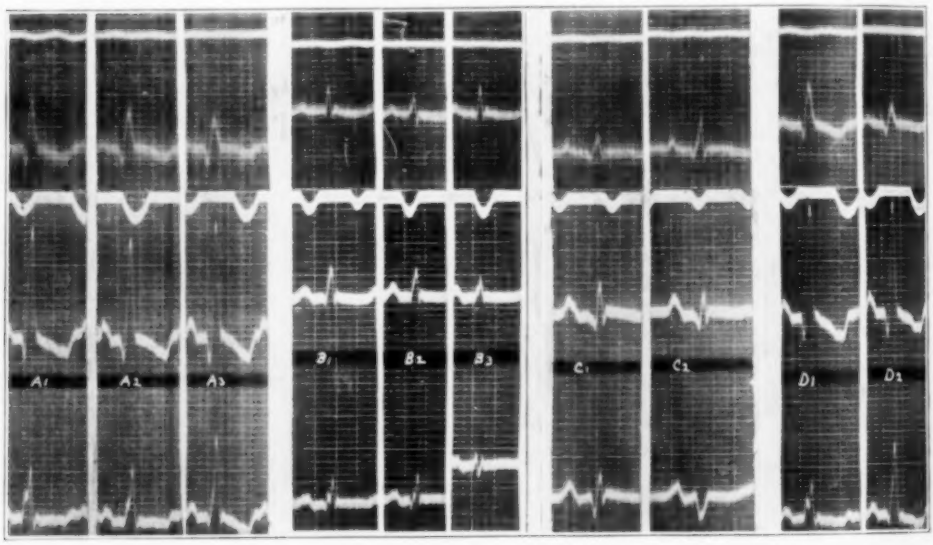

Fig. 5.—In these records the three leads were taken simultaneously. Lead I, the upper curve, was taken on one camera, while Leads II and III, the middle and lowest curves, were recorded together on another. Before the two slits a horizontal wire was raised and lowered at a rapid rate so that the vertical lines have no time value but they do mark synchronous points. Time is recorded between Leads II and III in one-fifth second. *A*1, normal; *A*2, heart pulled to the right; *A*3, heart pulled to the right and rotated to the left on the longitudinal axis; *B*1, normal; *B*2, heart pulled to the left; *B*3, heart pulled to the left and rotated to the right on its longitudinal axis; *C*1, normal; *C*2, heart rotated to the left on its longitudinal axis; *D*1, normal, and *D*2, heart rotated to the right on its longitudinal axis.

It would be of great interest and value to know just what degree of left or right sided hypertrophy could be obscured by the rotations involved in the shift of position occurring when the subject lies on the left or right side. Such an investigation would however involve the statistical

treatment of electrocardiograms in the various positions, roentgen-ray shadows of the heart, and a comparison of the ventricular weights secured at necropsy.

A recent paper by Dieuaide[6] is of interest in this connection. Dieuaide proposes diagnosing adhesive pericardial mediastinitis by the absence of variations in the electrocardiogram when the subject changes his position from side to side. Judging from our data it would be expected that no patient with adhesive pericardial mediastinitis would show variations due to change of body position if the adhesions were sufficient to anchor the heart; but on the other hand all patients failing to show variations with a shift of position could hardly be expected to have mediastinitis, the reason being that when the patient is turned to either side, the rotation of the heart around the longitudinal axis may exactly neutralize the effect of the rotation around the anterior-posterior

TABLE 5.—*Rotation to the Right and Left Around the Longitudinal Axis Only*

	Experiment	Electrical Axis, Degrees	R_1	R_2	R_3
Normal	22	64	2.5	5.8	3.3
Rotated right	"	—7	6.0	2.1	—3.3
Normal	25	68	3.3	8.0	5.0
Rotated right	"	—6	9.6	4.0	—5.8
Normal	28	61	5.5	10.0	5.5
Rotated right	"	16	8.5	6.7	—2.2
Normal	26	60	4.5	10.0	5.6
Rotated left	"	81	3.0	13.3	11.0
Normal	28	62	4.6	10.6	5.6
Rotated left	"	106	—3.1	7.5	10.6
Normal	30	53	7.8	13.9	5.6
Rotated left	"	72	4.4	12.2	8.3

axis, and the result in the electrocardiogram will be the same as if no movement has occurred.

The results obtained in our experiments with rotation around the longitudinal axis seem to bear quite directly on the theory of Groedel and Mönckeberg[7] as to the cause of hypertrophy curves obtained in various diseases of the heart. These workers found an inverted R in Lead I in such diseases as pulmonary insufficiency, pulmonary stenosis, open ductus arteriosis, tricuspid insufficiency, and in some mitral stenosis cases. In all of these diseases, it has been found at necropsy that the right ventricle hypertrophies, not by extending to the right, since it would then have to push aside the right auricle which is fixed by the venae cavae, but by rotating slightly around the axis of the cavae and then by extending up and to the left in the direction of the

6. Dieuaide, F. R.: The Electrocardiogram as an Aid in the Diagnosis of Adhesive Pericardial Mediastinitis, Arch. Int. Med. **35**:362 (March) 1925.

7. Groedel and Mönckeberg: Zentralbl. f. Herzkrankh. u. Gefässe. **5**:2, 1913.

pulmonary artery. This position throws the septum into the frontal plane, and places the left ventricle completely dorsal and the right ventricle completely ventral in relation to this plane. Obviously, this condition was practically duplicated by our rotation of the heart around its longitudinal axis, without displacement around the anterior-posterior axis.

The same authors have shown that a pendant heart may give the same electrocardiogram as a transverse heart, simply owing to this rotation around the longitudinal axis. In cases of left sided hypertrophy due to mitral insufficiency, aortic lesions or sclerosis of the blood vessels of the kidney, the growth of the left ventricle is described as rotating the heart to the right around its longitudinal axis, thus making the left ventricle more ventral in position, and always producing a strongly positive initial deflection of the electrocardiogram. Rotations of the ventricles around the longitudinal axis, whether due to experimental, physiologic, or pathologic causes, must obviously disturb the normal relationship of the muscle masses of both ventricles to the frontal plane. The projection of the electrical vectors on this plane of the electrocardiographic leads is, of course, also greatly modified, and in this fact is the fundamental reason for the variation in the electrocardiographic curves.

SUMMARY

1. Displacements of the heart around its anterior-posterior axis either to the right or the left as carried out experimentally do not give the curves anticipated according to the principle of the Einthoven triangle, or according to the accepted standards for right or left sided preponderance. The electrical axis may be either increased or decreased or remain the same.

2. If when the heart is displaced to the right or the left, a counter-rotation in the opposite direction around its logitudinal axis is brought about, the curves approach those of right and left sided preponderance, the electrical angle regularly increasing or decreasing as it should.

3. It is evident that the effects of mere displacement have been masked by rotation on the longitudinal axis. In proof of this it is found that, if the heart is held in its normal position and then rotated on its longitudinal axis, typical curves of right or left sided preponderance may be produced.

4. Either uncomplicated rotation to the right on the anteroposterior axis or rotation to the left on the longitudinal axis will give curves characteristic of right sided preponderance. The reverse conditions will give curves characteristic of left sided preponderance.

5. The importance of having the heart in the normal position for all electrocardiograms is emphasized. It seems clear that it is impossible to tell how much a change in position may affect the electrocardiogram or how much an abnormal electrocardiogram may be due to variations in position, since the result is due to the summation of different rotations. Variations in position may accentuate, neutralize or reverse the effects of a slight degree of hypertrophy. It is for this reason that, as Herrmann and Wilson insist, the influence of the relative weight of the two ventricles predominates only when the heart is greatly hypertrophied.

VITAL CAPACITY, RESPIRATORY FREQUENCY, PULSE RATE AND SYSTOLIC BLOOD PRESSURE IN HEART DISEASE

THEIR IMPORTANCE IN THE CLASSIFICATION OF PATIENTS*

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A satisfactory classification of patients with organic heart disease based on their ability to carry on physical activity would be of great value to every clinician. It is our purpose in this article to show that the consideration of the vital capacity of patients with heart disease, together with their respiratory frequency, pulse rate and systolic blood pressure, after climbing 30 feet of stairs in forty seconds divides them into three main groups. The form of exercise test used in this study differs entirely from that type of test in which the individual is exercised until dyspnea first appears, in that a definite time and weight lifting task is accomplished. In this study the reaction of the individual to a definite task is noted instead of only the amount of work that may be done to bring about dyspnea in the individual. It is hardly necessary to state that the results obtained by these two methods are not comparable.

The Association of Cardiac Clinics of New York recognizes the following classification of patients with heart disease:

Class I. Organic—able to carry on habitual physical activity.

Class II. Organic—able to carry on:

A. Slightly diminished physical activity.

B. Greatly diminished physical activity.

Class III. Organic—unequal to any physical activity.

Class IV. Possible—having doubtful murmurs, mainly accidental, possibly organic.

Class V. Potential—having a predisposing history.

Class I and Class II, A and B, are based on the ability of cardiac patients to carry on physical activity; however, up to the present time no uniform method has been described to aid us in grouping heart cases according to the foregoing classification. Various procedures are in use today. Some of these are based on the measurement of the vital capacity; others, on the pulse or systolic blood pressure reactions following different exercises, such as stair climbing, body bending, deep knee flexions and swinging of dumb-bells. The importance of completing

* From the Mineola Home for Cardiac Children, Irvington, N. Y., in the service of Dr. Robert H. Halsey.

uniform exercise has been recognized. Thus, there may be variations in the number of feet actually climbed or in the time allowed for climbing the same number of stairs; in the number of times the body bending exercises and the deep knee flexions are performed, and in the weight of the dumb-bells or in the time allowed for each swing. Obviously, comparable results cannot be expected since the actual effort required is not controlled by time or work to be accomplished.

Investigators have attempted to employ one or more of these tests as a means of determining the functional capacity of the heart, using either the estimation of the vital capacity or the time required for the pulse or systolic blood pressure to return to the rest levels.

The inferences drawn from these determinations are numerous and varied. Brittingham and White,[1] in studying the systolic blood pressure reaction after exercise, concluded that it may be of some value in determining the individual's tolerance for work. The results obtained, however, were not uniform in that cases with apparently no organic heart disease presented systolic pressure curves similar to those obtained in cardiac patients. Wilson [2] utilized the degree of distress and systolic pressure curves as a gage in estimating the exercise tolerance of children with heart disease, and found that exercise tolerance tests give important information which may be employed as a scientific basis for the proper regulation of the child's activities. In Propst's [3] series of cases with organic heart disease only 3 per cent. presented abnormal pressure reactions. He was more satisfied with the results obtained by following the changes in the pulse rate before and after exercise. Brady [4] feels that a pulse not returning to the preexercise level in three minutes following fifteen deep knee flexions should be viewed with suspicion.

Similarly, various observers have stated that there was no uniform relation between the vital capacity of the lungs and the condition of the heart in patients with heart disease. The work of Peabody and Wentworth [5] would indicate that there is a close relationship between the degree of dyspnea noted in heart disease and the vital capacity of the lungs. They found that in general patients with a vital capacity of 90 per cent. or more of the normal standard have little tendency to dyspnea.

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1. Brittingham, H. H., and White, P. D.: Cardiac Functional Tests, J. A. M. A. **79**:1901 (Dec. 2) 1922.

2. Wilson, May G.: Exercise Tolerance of Children with Heart Disease, J. A. M. A. **76**:1629 (June 11) 1921.

3. Propst, D. W.: Exercise Cardiac Functional Test in One Hundred Cases of Heart Disease, J. A. M. A. **82**:2102 (June 28) 1924.

4. Brady, William: The Anamnesis in Cardiovascular Disease, J. A. M. A. **70**:1449 (May 18) 1918.

5. Peabody, F. W., and Wentworth, J. A.: Clinical Studies of the Respiration, IV, The Vital Capacity and Its Relation to Dyspnea, Arch. Int. Med. **20**:443 (Sept.) 1917.

Patients with a vital capacity from 70 to 90 per cent. of the normal become dyspneic following unusual exertion and must restrict their daily activities, but may perform light work. Patients with a vital capacity of from 40 to 70 per cent. of the normal standard show marked dyspnea on slight exertion and are, as a rule, unable to work. Patients with a vital capacity of less than 40 per cent. of the normal are decompensated patients. Brittingham and White [1] report a low vital capacity in 100 per cent. of their patients with congestive heart failure, while, almost without exception, in those cases with no congestive failure a normal vital capacity was observed. Burton-Opitz [6] emphasizes that the vital capacity changes little in compensated cases. Wilson and Edwards [7] observed a reduction in the vital capacity in cardiac patients showing a diminished exercise tolerance. The group averages pointed to a relationship between the reduction in the vital capacity measurements and the degree of diminution in the exercise tolerance. Although this relationship has been observed in the group averages, no such definite relationship could be assigned to the individual cases.[8]

It is apparent that considerable difference of opinion exists with respect to the clinical value and to the proper interpretation of the results obtained when these tests are used as tests of the heart. Because of the marked variability noted, the majority of the tests have not won uniform approval and have been considered valueless by many clinicians. The majority of the investigators have made the error of using the tests as heart tests rather than as tests of the person with heart disease. It is obvious, from the experimental data cited and from our own observations, that not one of the tests can be considered a satisfactory or reliable heart test. However, when they are used collectively, with the object of testing the subject with heart disease, definite and valuable information is obtained.

Our study consisted of the estimation of the vital capacity at rest and the determination of the length of time required for the respiratory rate, pulse rate and systolic blood pressure to return to their preexercise level after the patients climbed 30 feet of stairs in forty seconds. All the patients tested were children between the ages of 6 and 16 years with definite organic heart disease due to the infection of rheumatic fever. The patients were ambulatory and showed none of the early symptoms of decompensation, such as precordial distress, edema of the ankles, or signs of pulmonary congestion. They presented a normal temperature and, as far as could be ascertained, were free from any

6. Burton-Opitz, Russell: Vital Capacity of "Cardiacs," J. A. M. A. **78**: 1686 (June 3) 1922.

7. Wilson, May G., and Edwards, D. J.: The Vital Capacity of the Lungs and Its Relation to Exercise Tolerance in Children with Heart Disease, Am. J. Dis. Child. **22**:443 (Nov.) 1921.

8. Wilson and Edwards (Footnote 7). Ziskin, Thomas: Vital Capacity as a Functional Test in Heart Disease, Arch. Int. Med. **35**:259 (Feb.) 1925.

other disease. The respiratory rate and the pulse rate were taken immediately after the exercise and at one minute intervals until the respiratory rate was within two points and the pulse rate within four points of the preexercise level. The systolic blood pressure was taken immediately after the exercise and at one-half minute intervals until it reached within 6 mm. of the pressure at rest. A series of ninety-six cases was studied. The results obtained are recorded in the table.

An examination of the table shows that the cases studied may readily be classified into three main groups. The patients in the first group show a vital capacity of not less than 90 per cent. of the normal and a return of the respiratory rate, pulse rate and systolic blood pressure to the rest level within two minutes' time. The patients in the second group show either a vital capacity of from 90 to 80 per cent. of the normal standard or an increase in the time required for any one of the factors concerned in the exercise tests to return to the preexercise level. This level was reached within three minutes' time. The patients in the third group show either a vital capacity of less than 80 per cent. of the normal or a period of time greater than three minutes required for either the respiratory rate, pulse rate, or systolic blood pressure to return to the preexercise level.

The patients coming under the first group show a vital capacity within normal limits and a return to the rest level in two minutes of all the factors studied in the exercise test. These children were able to carry on usual physical activity without showing signs of dyspnea or overactivity of the heart and accordingly did not need to be restricted in their daily routine. Cases classified in this way correspond to Class I cases of the classification of the Association of Cardiac Clinics. The patients in the second group show either a vital capacity between 90 and 80 per cent. of the normal or a period of time greater than two minutes, but not more than three minutes for either one of the other factors to return to the preexercise level. The members of this group usually presented varying degrees of dyspnea and exhaustion, or some overactivity of the heart following exertion caused by setting-up exercises, stairs climbing, etc. They may conveniently be placed in Class II A of the association classification. The children coming under the third group show either a vital capacity below 80 per cent. of the normal or require more than three minutes for any one of the other three factors to reach the rest level. The subjects in this group definitely presented signs of dyspnea, exhaustion, or overactivity of the heart after climbing 30 feet of stairs. These cases answer very favorably the description of the Class II B cases of the association classification. In our series eight belong to the first group, forty to the second and forty-eight to the third group.

Vital Capacity and Respiratory Frequency, Pulse Rate and Systolic Blood Pressure Before and After Climbing Thirty Feet of Stairs in Forty Seconds

Case	Diagnosis	Class	Vital Capacity Percentage of Normal	Exercise Test: Respiratory Rate At Rest	Respiratory Rate Minutes After Exercise 1	2	3	4	5	Pulse Rate At Rest	Pulse Rate Minutes After Exercise 1	2	3	4	5	Systolic Blood Pressure At Rest	Systolic Blood Pressure Minutes After Exercise 0	1	2	3	4	5
1	Mitral insufficiency	I	105	24	32	24	..	..	..	86	104	88	...	...	...	110	118	108	...	...	...	...
2	Mitral insufficiency and stenosis	I	102	20	28	24	..	..	..	92	100	70	...	...	...	114	142	130	120	...	...	...
3	Aortic insufficiency and mitral insufficiency	I	93	20	28	22	..	..	..	96	120	100	...	...	...	110	150	132	114	...	...	...
4	Mitral insufficiency	I	103	24	28	24	..	..	..	84	108	86	...	...	...	118	158	132	124	...	...	...
5	Mitral insufficiency	I	96	20	28	24	..	..	..	88	104	88	...	...	...	130	158	136	132	...	...	...
6	Aortic insufficiency	I	127	24	32	28	..	..	..	100	150	98	...	...	...	150	180	160	150	...	...	...
7	Mitral insufficiency and stenosis	I	98	20	28	24	..	..	..	98	124	102	...	...	...	106	132	118	110	...	...	...
8	Mitral insufficiency	I	92	24	28	24	..	..	..	84	120	76	...	...	...	134	162	148	140	...	...	...
9	Mitral insufficiency and aortic insufficiency	II A	88	24	28	24	..	..	..	84	100	80	...	...	...	122	180	150	130	122	...	...
10	Mitral insufficiency	II A	82	18	26	18	..	..	..	84	98	78	...	...	...	102	114	110	104	...	...	...
11	Mitral insufficiency	II A	80	18	30	22	20	..	..	82	82	...	...	...	...	90	108	106	98	94	...	...
12	Aortic insufficiency	II A	89	24	26	28	24	..	..	94	138	92	...	...	...	132	190	160	136	...	...	...
13	Mitral insufficiency and stenosis	II A	82	24	28	24	..	..	..	118	136	122	120	...	...	100	122	116	108	100	...	...
14	Aortic insufficiency and mitral insufficiency	II A	80	28	36	32	28	..	..	80	106	74	...	...	...	110	200	150	122	110	...	...
15	Aortic insufficiency, mitral insufficiency and stenosis	II A	85	24	28	26	..	..	..	84	102	82	...	...	...	110	136	120	116	112	...	...
16	Mitral insufficiency	II A	82	20	28	24	20	..	..	94	116	96	...	...	...	132	158	140	134	...	...	...
17	Aortic insufficiency and stenosis, mitral insufficiency and stenosis	II A	90	24	36	32	28	..	..	78	100	76	...	...	...	126	138	124	...	...	...	...
18	Aortic insufficiency, mitral insufficiency and stenosis	II A	88	24	28	24	..	..	..	82	98	78	...	...	...	124	150	134	130	...	...	...
19	Aortic insufficiency and stenosis, mitral insufficiency and stenosis	II A	81	24	32	28	24	..	..	92	126	100	94	...	...	130	164	160	148	136	...	...
20	Aortic insufficiency, mitral insufficiency and stenosis	II A	89	24	28	24	..	..	..	86	101	84	...	...	...	98	168	140	118	104	...	...
21	Aortic insufficiency, mitral insufficiency and stenosis	II A	80	20	28	24	22	..	..	88	104	84	...	...	...	122	158	138	124	...	...	...
22	Mitral insufficiency	II A	80	20	32	28	22	..	..	82	94	80	...	...	...	96	118	120	100	...	...	...
23	Aortic insufficiency and stenosis, mitral insufficiency and stenosis	II A	81	20	28	24	22	..	..	90	118	108	92	...	...	140	162	156	140	...	...	...
24	Aortic insufficiency, mitral insufficiency and stenosis	II A	89	20	28	24	20	..	..	104	140	106	...	...	...	116	134	130	116	...	...	...
25	Mitral insufficiency	II A	85	18	28	24	20	..	..	78	98	90	80	...	...	116	144	130	114	...	...	...
26	Mitral insufficiency	II A	90	24	36	32	26	..	..	82	102	80	...	...	...	136	160	148	134	...	...	...
27	Mitral insufficiency and stenosis	II A	88	20	30	28	24	..	..	82	104	82	...	...	...	92	102	100	94	...	...	...
28	Aortic insufficiency and mitral insufficiency	II A	84	20	28	24	..	..	..	70	104	72	...	...	...	106	138	118	110	...	...	...
29	Mitral insufficiency	II A	82	22	26	24	..	..	..	88	130	90	...	...	...	110	124	120	116	112	...	...
30	Aortic insufficiency and mitral insufficiency	II A	85	24	32	28	24	..	..	82	106	78	...	...	...	140	200	180	150	142	...	...
31	Mitral insufficiency and stenosis	II A	88	24	28	24	..	..	..	84	120	78	...	...	...	112	136	130	118	112	...	...
32	Aortic insufficiency and stenosis, mitral stenosis	II A	81	24	28	24	..	..	..	92	130	98	90	...	...	134	162	150	140	134	...	...
33	Aortic insufficiency, mitral insufficiency and stenosis	II A	95	24	28	24	..	..	..	90	102	90	...	...	...	120	150	138	128	122	...	...
34	Mitral insufficiency and stenosis	II A	89	20	32	26	22	..	..	84	108	90	86	...	...	92	102	92	...	...	...	...
35	Mitral insufficiency	II A	80	16	22	22	18	..	..	82	112	84	...	...	...	98	144	130	104	...	...	...
36	Mitral insufficiency	II A	87	24	26	24	..	..	..	88	100	84	...	...	...	98	130	116	98	...	...	...
37	Mitral stenosis	II A	80	20	26	28	24	..	..	90	140	116	88	...	...	128	148	140	134	...	...	...
38	Mitral insufficiency and stenosis	II A	82	24	28	24	..	..	..	88	128	86	...	...	...	118	152	146	130	122	...	...
39	Aortic insufficiency	II A	80	24	36	28	..	..	..	88	128	78	...	...	...	138	188	148	140	...	...	...
40	Aortic insufficiency	II A	85	24	32	24	..	..	..	92	138	110	94	...	...	140	182	172	158	144	...	...
41	Aortic insufficiency and mitral insufficiency	II A	82	24	28	24	..	..	..	86	108	88	...	...	...	116	138	130	...	...	...	...
42	Mitral insufficiency	II A	80	20	24	20	..	..	..	96	120	108	92	...	...	116	140	113	118	...	...	...

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When we undertook our study we were aware of the lack of a uniform method of classifying patients with organic heart disease. We were likewise aware of the criticisms directed at the various tests employed as cardiac function tests or exercise tolerance tests. In our work we used practically the same tests utilized by other observers; however, we attached a different significance to them. The majority of the investigators employed either the measurement of the vital capacity or the pulse and systolic pressure curves as tests of the heart. The results were generally disappointing, and for that reason the tests were considered as being of little or no value by many chinicians. It is quite obvious that these tests are not heart tests. It is well known that the vital capacity, respiratory frequency, pulse rate and systolic pressure are influenced by fright, excitement, neurotic tendencies and in some degree by the physical condition of the patient. For that reason many non-cardiac patients may present the same reactions observed in heart cases. This fact, however, does not prove that the tests are absolutely valueless in the study of patients with heart disease. When used for the purpose of testing the individual with cardiac disease, rather than of testing the heart of the patient, helpful information is obtained. The tests must be regarded then as tests of a subject and not as tests of the subject's heart. On the basis of the vital capacity and the response of the patient to exercise as measured by the respiratory frequency, pulse rate and systolic pressure, these cases group themselves into the three main classes described above regardless of the valvular damage.

A close analysis of the results presents another important point: the lack of a general parallelism between the various factors studied. It will be noted that many cases presenting a prolonged fall in the pulse rate may have a normal blood pressure curve and vice versa. Other cases showing a prolonged fall in either the pulse rate or systolic pressure have a vital capacity within normal limits, or a low vital capacity may be obtained with a normal pulse and systolic pressure curve. That would indicate that the estimation of the vital capacity alone, or the determination of either the respiratory frequency, pulse rate or systolic pressure alone is not a reliable test of the subject but that complete information concerning the case can only be obtained by a utilization of all the observations.

The method of classification we have adopted can be defined clearly and is not influenced by the personal equation of the persons performing the tests. It affords a more uniform way of classifying patients with heart disease than has previously been described. Such a classification enables the physician to regulate and prescribe more intelligently the physical activity of the patient with heart disease.

SUMMARY AND CONCLUSIONS

On the basis of the measurement of the vital capacity of ninety-six children with organic heart disease, together with their response to the climbing of 30 feet of stairs in forty seconds as measured by the respiratory frequency, pulse rate and systolic blood pressure, these cases can be conveniently grouped in three main classes corresponding to Class I, Class II A and Class II B of the classification of the Association of Cardiac Clinics. Because of the lack of a general parallelism between the results of the various tests, it is evident that one test alone does not furnish a satisfactory basis for making a classification of patients with heart disease. These tests cannot be considered cardiac function tests but are of great assistance in the intelligent care of children with organic heart disease.

CLINICAL DIAGNOSIS AND THE INTESTINAL FLORA *

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For clinical purposes, the determination of the intestinal flora should be made in the shortest possible time. The work takes forty-eight hours, which is the shortest average time for giving the findings required for such an examination. This is not intended for a detailed bacteriologic study on all bacteria present in the flora, but consideration is centered on a few bacterial groups whose dominance is directly responsible for the character of the flora. The elaborate study of intestinal bacteriology advanced by McNeal,[1] Meyer and others [2] is rather cumbersome for clinical diagnosis, while the method of Rettger and Cheplin,[3] although simple, does not cover the entire field. In developing the method, I have carefully scrutinized cultural and morphologic characteristics of the dominant bacteria in question, thereby making it possible to draw accurate interpretation of the floral findings.

The bacteria in the stool are numerous and constitute from one fourth to one third of fecal dry matter. There are at least 100 different kinds of bacteria present. The morphologic and cultural characteristics of some of these are as yet unknown to us. The isolation of each of these bacteria requires much time, and from the clinical standpoint is not worth it. My aim is, therefore, not to determine one bacterium or two, but to diagnose the intestinal flora as a whole whether it be of fermentative, putrefactive or mixed type.

The bacteriologic examination of the stool consists of cultural and microscopic technic, and the character of the flora is determined by the findings, the emphasis being laid on the cultures. In other words, the diagnosis is made from the summarized results by checking one against the other. In many cases the microscopic examination helps to substantiate the cultural findings.

In this study the intestinal bacteria are classified under the following groups:

(*a*) Colon-like bacteria (*Bacillus coli, B. proteus-vulgaris, B. aerogenes, B. enteriditis, B. fecalis-alkaligenes*, etc.);

(*b*) Acidophilus-like bacteria (*B. acidophilus, B. bifidus*);

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* From the clinical laboratories, Battle Creek Sanitarium.

1. McNeal et al.: J. Infect. Dis. **6**:103; 571, 1909.
2. Morris, G. B.; Porter, R. L., and Meyer, K. A.: J. Infect. Dis. **25**:349 (Nov.) 1919.
3. Rettger and Cheplin: A Treatise on the Transformation of the Intestinal Flora, New Haven, Conn., Yale University Press, 1921.

(*c*) Spore-bearing bacteria (*B. welchii, B. putrificus; B. butyricus,* etc.);

(*d*) Gram-positive cocci (*Streptococcus fecalis,* micrococci, diplococci and enterococci), and

(*e*) Yeasts.

For diagnostic purpose the intestinal flora is classified under the following headings:

(*a*) Fermentative. This type contains a large percentage of *Bacillus acidophilus,* and is excellent in every respect. Fermentation does not imply an excessive gas production. The percentage of coli-like organisms is very small.

(*b*) Semifermentative. This type contains a fairly large number of *Bacillus acidophilus* with some coli-like bacteria with or without streptococci.

(*c*) Mixed. This type is a congregation of all sorts of bacteria. A small percentage of *Bacillus acidophilus* and *Bacillus welchii* are often present in this type.

(*d*) Semiputrefactive. This type shows the dominance of putrefactive bacteria with or without *Bacillus acidophilus.*

(*e*) *Putrefactive.* This type is characterized by being distinctly putrefactive, dominated by the *Bacillus coli* group and spore-bearing without the presence of *Bacillus acidophilus.* The bacterial metabolism is strongly proteolytic.

TECHNIC OF BACTERIOLOGIC ANALYSIS

Fecal Suspension.—This is prepared by thoroughly mixing about a pea-sized stool or 1 c.c., if liquid, with 10 c.c. of sterilized physiologic sodium chlorid solution to make a uniformly homogeneous emulsion. A small ball of cotton should be inserted clear to the bottom of the tube to serve as an automatic filter. The supernatant suspension thus made is devoid of food remnants, which often interfere with technic.

Microscopic Examination.—(*a*) Smear: The uniform smear is made from the suspension by means of a platinum wire, and dried either by flame or air. The slide is stained according to the Gram method.

(*b*) Gram Stain Classification of Bacteria: This is made by examining at least from ten to fifteen microscopic fields with the aid of a square field ocular, and calculating the percentage of gram-positive and negative. Special attention is paid to the presence of acidophilus-like organisms that are of polymorphous rod shape. If there is dominance of a particular type of bacteria, note is made by the plus sign. For the convenience of the study, the following bacterial groups are placed in the working blank: colon-like bacteria, acidophilus-like bacteria, spore-

bearing bacteria, streptococci and yeasts. Under these headings the following bacteria are gram-positive: *B. acidophilus, B. welchii, B. butyricus, B. putrificus,* streptococci and diplococci. Most other bacteria are gram-negative.

Microscopic Morphology of B. Acidophilus: This should be carefully studied, as the determination of the flora depends entirely on the findings of this particular organism. It is a gram-positive rod and polymorphous. They generally appear singly, but often in pairs or in a short chain. The single bacillus is a slender rod, often slightly tapering at both ends and resembling a part of the corkscrew-like formation of spirocheta, and again it may present almost a coccus-like appearance. The smear made from an old culture often fails to retain gram iodin, and gives an appearance of a gram-negative organism. *B. acidophilus* does not possess spore, capsule or flagella. They are immotile.

Morphology of Colon-Like Bacteria: All the gram-negative bacteria of every description are included in this category.

Morphology of Spore-Bearing Type: They are short and thick rods, usually found in pairs but often singly. The consideration of butyricus and putrificus should be more or less dependent on the cultural findings.

The higher the percentage of gram-positive bacteria, as a rule, the better the condition of the intestinal flora, while with the higher percentage of gram-negative, the worse the condition, provided the cultural findings coincide with the microscopic. A higher percentage of gram-positive, therefore, does not necessarily indicate, in all cases, fermentative flora, as there are often cases in which the microscopic fields are crowded with gram-positive bacteria of the spore-bearing type and diplococci. However, if there is a predominance of gram-positive bacteria coupled with good cultural findings, it is safe to make a favorable diagnosis of the flora. The microscopic test is not, therefore, an accurate method, and should be wholly or partially dependent on the cultural findings. The higher percentage of gram-negative bacteria is always found in putrefactive flora. The approximate percentage of gram-positive bacteria in different types of intestinal flora is: Fermentative, from 75 to 100; semifermentative, from 55 to 70; mixed, from 35 to 50; semiputrefactive, from 10 to 30, and putrefactive, from 5 to 20.

Cultural Examination.—Litmus Milk Culture: The test tube used for this purpose is 1 inch (2.5 cm.) in diameter and 6 inches (15.2 cm.) in length. A small inverted tube is inserted in order to determine the percentage of gas formation. The media is distributed in culture tubes, and sterilized in the autoclave at 15 pounds pressure for 20 minutes; 1 c.c. of fecal suspension is inoculated into milk culture, and incubated at 37 degrees C. for 48 hours.

Reaction: The reduction of litmus by the acidity formed by bacteria is designated by plus signs according to the degree of acidity. Whether the flora is putrefactive or fermentative, the reaction is always acid except in the cases of special types of bacteria, such as *B. typhosus*, *B. dysenteriae* and *B. fecalis-alkagenes*. The longer the incubation, the higher the production of acidity. *B. coli* and *B. acidophilus* as well as *B. welchii* intensify the acidity in prolonged incubation.

Coagulation: This is classified under the following headings:

(*a*) Cheeselike or stormy fermentation. The coagulated milk presents lattice-like furrows. If accompanied by floating gas bubbles with a large amount of whey, the presence of *B. welchii* is suspected. This is confirmed by a special test described later.

(*b*) Soft curd. Yellowish soft curd with or without whey formation is indicative of putrefactive flora dominated by *B. proteus vulgaris*. If such a culture is left incubated for a longer period, a complete peptonization takes place.

(*c*) Retraction. Complete retraction of the curd is a putrefactive process. Partial retraction is often found in any type of flora. The interpretation varies according to other findings in milk.

(*d*) Firm massive coagulation. The firm massive coagulation with whey indicates the fermentative type.

If the flora is distinctly dominated by *B. acidophilus*, the coagulation is slimy at twenty-four hours' incubation. On further incubation, the acidity of the milk increases owing to the formation of lactic acid from lactose, and consequently there is a production of whey. The amount increases as the incubation is prolonged.

Whey: The amount of whey is designated by a plus sign. The test tube is tilted slightly to measure the approximate amount.

The interpretation of whey varies according to other findings. If accompanied by stormy fermentation it indicates the presence of spore-bearing bacteria, notably *B. welchii;* with firm massive coagulation, the presence of the fermentative type is indicated. The complete peptonization is a putrefactive process.

Gas Formation: The inner tube takes the place of an ordinary fermentation tube used elsewhere. It is less expensive, and for routine procedure it answers the purpose just as well. The whole length of the tube is considered as 100 per cent. If one half the tube is filled with gas, it is considered as 50 per cent.; one fourth, 25 per cent.

The amount of gas in the fermentative type is probably low, ranging from 0 to 20 per cent., while in the putrefactive flora it is higher, often almost 100 per cent.

Summarizing the findings obtained from milk culture in the typical cases, putrefactive flora is characterized either by stormy fermentation

Type	Putrefactive	Semiputrefactive	Mixed	Semifermentative	Fermentative
Litmus milk	Stormy fermentation or soft curd; floating gas bubbles; complete peptonization; large percentage of gas in inner tube; slight reduction of litmus	Soft curd with or without whey; moderate percentage of gas; partial retraction, accompanied by stormy fermentation	Soft curd or firm coagulation, with or without whey; moderate percentage of gas; fair reduction of litmus	Firm massive coagulation with moderate amount of whey; small percentage of gas; reaction acid	Firm massive coagulation with whey; 0-10 per cent. of gas in inner tube; reaction distinctly acid
Confirmatory test	B. welchii positive.....	B. welchii positive	B. welchii positive or negative	B. welchii negative	B. welchii negative
Lactose broth	Turbidity, with scum and pellicle or sediment; gas in inner tube, over 60 per cent.	Turbidity, with scum, pellicle or sediment; gas in inner tube, 40-60 per cent.	Turbidity, with or without scum; pellicle sediment moderate; gas in inner tube, 25-40 per cent.	Turbidity, with or without scum or pellicle; gas 5-25 per cent. according to the number of B. coli	Turbidity slight, with or without scum or pellicle; gas 0-10 per cent. according to the number of B. coli
Veillon tube	Large percentage of gas chiefly of anaerobic type; no acidophilus colony	Large percentage of gas consisting of colon and welchii types, with or without acidophilus colony	Fair amount of gas dominated by coli type; some acidophilus colonies	No gas or little of B. coli group; moderate number of acidophilus colonies	No gas formation; abundant acidophilus colonies
Petri plate	No acidophilus colony present; other colonies numerous and variable in types	With or without acidophilus colony; other colonies are quite numerous and variable	Some acidophilus colonies; other colonies fairly variable	Many acidophilus colonies; a few other types	Abundant acidophilus colonies; a very few other types
Microscopic examination	Gram-positive, 0-30 per cent.; predominance of coli group with spore-bearers and c o c c i; gram-negative abundant	Gram positive, 30-50 per cent.; a few rod-shaped acidophilus-like bacilli; spores often scattered; B. welchii present	Gram positive, 35-50 per cent.; acidophilus-like bacilli mixed with coli type; B. welchii in small number or absent	Gram positive, 55-70 per cent.; presence of many acidophilus-like bacteria; total absence of spore-bearers	Gram positive, 75 per cent. up; presence of abundant acidophilus-like bacteria with a few coli group; no spore-bearers
Macroscopic examination	Scybala or formed; liquid or semiliquid; putrid, hydrogen sulphid, ammonia or butyric odor; dark brown; mucus often present, with or without blood	Formed or liquid; putrid odor; dark brown; mucus often present, with or without blood	Partly formed or mushy; no odor or slightly putrid; color variable; with or without mucus or blood	Partly formed or mushy; no odor or sour; green or yellow; no mucus; no blood	Fluffy, mushy or partly formed; sour or no odor; green or yellow; no mucus; no blood
Chemical tests	Reaction alkaline, acid or neutral Occult blood often present	With or without occult blood	Occult blood seldom present	Occult blood negative	Occult blood negative
Parasites	Present or absent.....	Present or absent	Absent	Absent	Absent

or yellow soft curd with considerable whey and gas bubbles, accompanied by 40 per cent. or more of gas in the inner tube. Fermentative flora shows a firm massive coagulation with some whey and a small percentage of gas or none at all in the inner tube with a distinctly acid reaction. An analysis of the types of flora is given in the accompanying table. Emphasis is therefore placed chiefly on the types of coagulation and of the peptonizing process.

One Per Cent. Lactose Broth: The reaction is adjusted to 0.7 per cent. of acidity according to an ordinary titration method, and the mediums are distributed in test tubes. The small tubes are inserted as in the milk culture for a similar purpose. It is autoclaved at 15 pounds pressure for twenty minutes. One-half cubic centimeter of fecal suspension is inoculated into each broth culture and is incubated at 37 degrees C. for forty-eight hours.

Turbidity: This is designated by plus signs according to its degree. The presence of the coli group, streptococci and enterococci induces an intense turbidity, while the flora dominated by acidophilus shows a smaller degree of turbidity.

Formation of Scum, Sediment and Pellicle: In the putrefactive type, these formations are noticeable especially if dominated by the coli group and spore-bearing bacteria. Sediment is observed when the streptococci group plays a dominant part. In the fermentative type, their formation as a rule is scarce, except in the case of a luxuriant growth of yeasts when a thick pellicle frequently develops.

Gas Formation: The percentage of gas is computed as in the case of a milk culture. In the putrefactive type, the percentage always increases and often reaches as high as 90 per cent. If there is over 60 per cent. of gas in the broth culture coupled with the characteristic appearance of a stormy fermentation in the milk culture, it is safe to determine the dominance of *B. welchii*. In the fermentative type, in which *B. acidophilus* plays an extensive part, the gas formation is reduced to a minimum. The hydrogen ion concentration of the mediums is brought to such an extent that the growth of the gas forming bacteria is partially or totally suppressed owing to the excessive evolution of acetic and lactic acid by aciduric bacteria.

Summarizing the findings obtained from the broth culture, we may say that the putrefactive type is characterized by the presence of intense turbidity with the formation of a scum and pellicle accompanied by a large percentage of gas in the inner tube. Over 60 per cent. sometimes indicates the presence of *B. welchii*. The fermentative type shows turbidity to a small extent with or without scum or pellicle and accompanied by a small percentage of gas.

Veillon Culture: A tubing 12 inches (30.4 cm.) in length is used for the culture. One end of the tube is tightly plugged with an unper-

forated rubber stopper, and the other end with a ball of cotton. The medium used is 1 per cent. lactose agar. The reaction is adjusted to 0.7 per cent. of acidity. The tube is filled with medium 9 inches (22.8 cm.) in depth and is sterilized in the autoclave at 15 pounds pressure for twenty minutes. One loopful of suspension is inoculated after the medium is cooled down to 42 degrees C., and the tube is tilted back and forth rather quickly in order that the inoculum will diffuse through the entire tube. The tube is dipped into cold water after the inoculation and is incubated at 37 degrees C. for from twenty-four to forty-eight hours. When the tube is placed in the incubator, a horizontal position is preferable for the culture to maintain uniform distribution of growth of gas forming and non-gas forming bacteria.

The Veillon culture was originated by Veillon[4] to determine the anaerobic growth, but for this purpose the tube answers three conditions: It favors (1) anaerobic bacterial growth, especially stormy fermentation of *B. welchii;* (2) the gas formation of facultative anaerobic bacteria, namely, those of colon-like organism, and (3) non-gas formation of *B. acidophilus.* If the deeper part of the medium is filled with big gaps, the presence of *B. welchii* can be suspected. In many instances, the gas evolved by the fermentative activity of *B. welchii* is so vigorous as to push the plug clear up to the top and break the medium asunder, as shown in Figure 2. The small bubbles of gas present throughout the culture are of *B. coli* and *B. aerogenes.* If there is no gas formation at all and the culture is occupied by many small fuzzy colonies, mostly microscopic, and other colonies of different shapes, it is safe to conclude that there is a decided predominance of non-gas forming bacteria. Some of these colonies are those of *B. acidophilus.*

Summarizing the findings obtained from Veillon culture, we may say that in the putrefactive type of flora there is a large amount of gas, especially of anaerobic type; in the mixed type there is a large amount of gas chiefly of colon-like bacteria with acidophilus colonies scattered throughout to a certain extent, and in fermentative type, there is no gas formation, but many minute fuzzy colonies of *B. acidophilus.*

In order to ascertain the identity of *B. acidophilus* colonies, the plate is made from the same medium as the foregoing or preferably 2 per cent. dextrose agar. This will enable the examiner to eliminate the colonies of other non-gas forming organisms.

Lactose or Dextrose Agar Plate: A fecal suspension, 0.5 c.c., is inoculated into the medium, and is poured into the plate. The streak method is not desirable for this particular examination. Two aerobic plates are prepared for each specimen, and incubated for forty-eight hours at 37 degrees C.

4. Veillon: Arch de méd. expér. et d'anat. Path. **10**:517, 1898.

The plate is made primarily for the determination of colonies of *B. acidophilus*. The colonies of *B. acidophilus* are different for each individual, and at different times in the same individual. There are no corresponding colonies in all the specimens examined. Thus, briefly, so far as my experience goes with this particular organism in regard to its characteristic colony formation, there are at least the following varieties:

Fimbriated type. It is characterized by a microscopic fuzzy colony of unusually compact form, resembling bits of wool interlaced with radiating threads. The colony resembles that of *B. tetanus*. Under this group, there are several subdivisions:

(*a*) Irregular shaped nucleus, dense or comparatively transparent with numerous fimbriations.

(*b*) Oval or round colonies with few or numerous fimbriations. The nuclear matter is somewhat granular.

(*c*) A very small colony, usually irregularly shaped, and at times slightly triangular with a few fimbriations. When this species is being examined, care should be taken not to confuse it with the artefact present in the plate.

(*d*) Conglomerate type with chains of two, three or several colonies, each having a sort of bottle shaped structure with a few fimbriations. The conglomeration is mostly longitudinal, but seldom transverse.

Nonfimbriated type. It is characterized by an oval or round colony without fimbriation. It is also microscopic, and if we carefully focus very short fimbriation may sometimes be detected, but not always. Whether or not these two main types of colonies are separate entities has not been fully brought out. I incline, however, to the belief that they are the same except under different concentrations of agar. Thus, if the agar is concentrated higher than 2.5 per cent., the pressure is brought to bear on the colonies to such an extent that the characteristic fimbriation may not be recognized. The hydrogen ion concentration of the medium as well as that of the fecal suspension is probably another important factor to be considered in this connection.

The percentage of *B. acidophilus* colonies is taken in proportion to the number of other colonies present in the plate. For accurate work, different dilutions should be prepared to facilitate the work. As the dilution increases, the number of colonies present becomes less, and the computation of the percentage of the acidophilus colonies can be made very easily. For instance, if there are 100 mixed colonies present, and ten are those of *B. acidophilus*, the percentage of the latter is 10. It is necessary to examine at least ten different microscopic fields on the plate, and make the average count of percentages. For routine purposes, the percentage of *B. acidophilus* colonies is conveniently designated by few, many and abundant.

The study is also made of the relationship of the various kinds of colonies with the type of the intestinal flora. Thus, in the putrefactive type, there is wide variation—a congregation of different types of bacteria, while in the fermentative type, the variety is reduced. In other words, the reduction of the variety of colonies present means a step by which the improvement of the flora takes place.

Summarizing the findings obtained from the plate, we may say that in the putrefactive type there is no acidophilus colony present and the variety of colonies is numerous, while in the fermentative type there are numerous acidophilus colonies with a few other kinds of colonies on the plate.

Confirmatory Test for B. Welchii: Litmus milk is used for the culture. About 5 c.c. of the medium is distributed into each tube, and a small amount of liquid petrolatum is added in order to make the culture favorable for anaerobic growth. Then it is sterilized at 15 pounds pressure for twenty minutes. Fecal suspension, 0.5 c.c., is inoculated

Fig. 1.—Various colonies of Bacillus acidophilus (sketch).

into the tube, and is heated in a water bath at 80 C. for twenty minutes to kill off vegetative forms of flora. This is incubated at 37 C. for two days.

If *B. welchii* is present, characteristic stormy fermentation takes place by the breaking up of the coagulated casein accompanied by the butyric odor. The evolution of gas bubbles can be detected by shaking the tube gently.

The findings in milk, broth and Veillon cultures can be confirmed well by employing the foregoing method. In case there is a slight doubt as to the character of the gas formation in the Veillon tube, this test will help to differentiate *B. welchii* from the gas formation caused by *B. aerogenes* or its allied bacteria.

Although it is generally admitted that *B. welchii* is a strictly fermentative bacteria of saccharolytic type, as advanced by Rettger,[5] its

5. Rettger: J. Biol. Chem. **11**:71, 1906.

presence in the cultural and microscopic examination is always indicative of putrefactive flora. In all the decisively fermentative type of flora there is hardly any *B. welchii* present. In the combination of coli group bacteria with *B. welchii*, the putrefactive process is very much augmented. According to Herter,[6] *B. welchii* is one of the most important factors of intestinal putrefaction, being responsible for the so-called saccharobutyric fermentation. As the flora gradually improves, the percentage of *B. welchii* and other spore-bearing bacteria gradually decreases. This has been proved time after time in the examination. The increase of the percentage of *B. acidophilus* is almost directly proportional to the decrease of that of *B. welchii*. In broth, the percentage of gas in the inner tube is greatly diminished, and in milk culture there is no stormy fermentation. The most striking change takes place in the Veillon tube in which there is a total disappearance of anaerobic gas formation characteristic of *B. welchii*. Microscopically, the fermentative flora present no typical morphology of *B. welchii*, and instead the fields are covered with gram-positive rods of the acidophilus group. In the intestinal flora *B. welchii* and *B. acidophilus* are the two antagonistic organisms; the presence of one is inimical to the other. When *B. welchii* is suppressed, *B. acidophilus* is the dominant organism to take its place. I agree with Meyer and others that in fermentative flora where there is no *B. welchii* present. The theory of bacteriophage has been recently advanced by d'Herelle,[7] and it is my belief that in some future time this interesting phenomenon can well be brought out in dealing with the relationship between these two organisms for the determination of intestinal flora.

I placed streptococci, diplococci and micrococci of any variety under the heading of gram-positive cocci, because they are very similar in their significance in the determination of flora. Torrey [8] asserts that a high casein or milk diet stimulates the growth of saprophitic streptococci and diplococci. Among the streptococci present, the brevis type is the most prevalent. According to Andrew and Horder,[9] this short type is *Streptococcus fecalis*, which ferments lactose, saccharose and mannite but not ruffinose. The significance of this type in the intestinal flora has not yet been definitely brought out, but they often are present in a large number of diarrheal cases secondary to protozoan diseases, or any other intestinal disorder favorable for the production of diarrhea. The hemolytic type is rarely found in the stool. If present, it may be the result of metastasis due to focal infection in the upper respiratory tract. It is undeniable in diarrhea that the number of diplococci is very much

6. Herter: Common Bacterial Infection of Digestive Tract, New York, 1907.
7. D'Herelle: Bacteriophage, translated into English, 1922.
8. Torrey, J. C.: J. M. Res. **39**:415 (Jan.) 1919.
9. Andrew and Horder: Lancet **2**:708, 1906.

increased, especially of the enterococci type described as *Micrococcus ovalis* by Thiercelin.[10] The number of diplococci is often increased in the arthritic cases secondary to focal infection, and in such the fields are often crowded with gram-positive diplococci, the number being approximately 90 per cent.

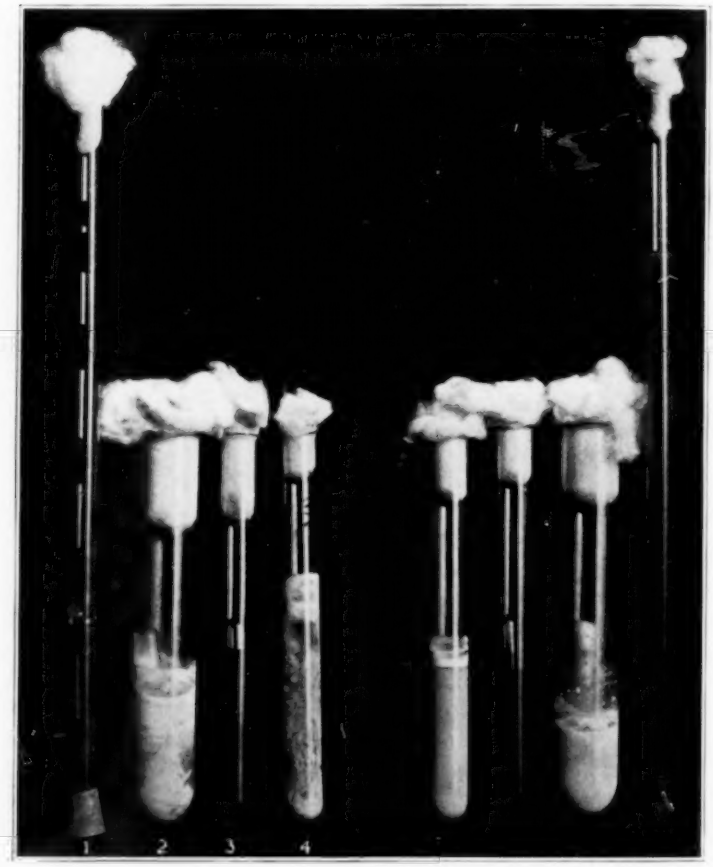

Fig. 2.—Cultural findings of intestinal flora; first group of tubes of putrefactive type, second of fermentative type. 1, Veillon tube; 2, litmus milk; 3, 1 per cent. lactose broth, and 4, milk for confirmatory test for Bacillus welchii.

Yeasts do not bear any significance in interpreting the character of intestinal flora. They are found as frequently in the putrefactive type as in the fermentative type. So far as my experience goes with the

10. Thiercelin: Compt. rend. Soc. de biol. **55**:269, 1899.

organism, there is no ground for the belief that the fermentative process is favored by their presence. They are often found in large numbers in a diarrheal stool. This, however, can be accounted for by an exaggerated peristalsis in these cases, appearing thus in the specimen without having undergone the destructive process in the digestive tract.

MACROSCOPIC AND CHEMICAL FINDINGS IN RELATION TO BACTERIAL ANALYSIS

The chapter will not be complete without touching on the rôles played by macroscopic and chemical findings in corroborating bacterial analysis. They often contribute more or less important data on the interpretation of the intestinal flora.

Amount of Stool.—The amount of the stool has nothing to do with the types of intestinal flora, except in the case of constipation, especially of the atonic type. Here the quantity of the stool is much diminished owing to the excessive absorption by the intestinal mucus. The number of bacteria also is generally reduced, and the flora chiefly consists of the putrefactive bacteria. The aciduric type cannot exist in any obstructions along the intestinal tract favorable for chronic constipation.

Color.—A dark brown suggests the putrefactive type of flora. The presence of this color is often characteristic of the meat regimen responsible for the condition. In green stools characteristic of the vegetable diet, putrefactive processes are very much lessened, while in the yellowish stools of the milk regimen the fermentative flora is often found.

Consistency.—The scybalic stool harbors putrefactive bacteria. The fermentative type is mostly found in partly formed or mushy consistencies. Semiliquid and liquid types are not of desirable form so far as the character of the flora is concerned. In the latter, bacterial congregation is very numerous both in quality and quantity.

Odor.—The odor of the stool has more to do with the interpretation of the flora than all other physical examinations put together. If the examiner accurately conducts his olfactory sense, the determination of flora is partially or wholly made before the bacteriologic examination is completed. The putrefactive type imparts an offensive odor owing to the presence of indol, skatol and mercaptan, particularly methyl mercaptan, as well as ammonia and hydrogen sulphid. The butyric acid odor is characterized by saccharobutyric fermentation in the flora dominated by *B. welchii*. The fermentative type is characterized by either sour or non-odor. The sour odor is due to the liberation of acetic and lactic acid by the activities of aciduric bacteria, which often partially or wholly inhibit the growth of purely alkaline or putrefactive bacteria. In a mixed type the odor varies according to the diet taken or the type

of bacteria dominant in the flora. Thus, in this type bacterial antagonism and symbiosis are at their height. The non-odor that often prevails in a putrefactive stool is probably due to excessive absorption of toxic substances by intestinal mucus, and the feces are usually scybalic. The reduction of the quantity of putrefactive by-products, therefore, means the betterment of the flora, and consequently that the odor of the stool is less offensive.

Reaction.—The reaction varies according to the kinds of diet taken. In a strictly fruit regimen the reaction is acid, while in a meat regimen alkalinity prevails. In a carbohydrate regimen, the reaction is often acid. In my study, an acid reaction does not necessarily indicate a good flora, while the same can be said in regard to the alkalinity of the putrefactive flora. Robinson [11] concluded that the hydrogen ion concentration of the intestinal content has no relation to the type of the bacterial flora.

Mucus.—The fermentative type is seldom found in the stool in which mucus is detected in large quantity. The presence of mucus always interferes with the process of transformation. Mucus is an albuminous substance, and favors the development of putrefactive bacteria. The presence of mucus, therefore, hinders the progress of the intestinal transformation. In cases of mucous colitis and other inflammatory and infectious diseases, mucus can be detected either separately or mixed with the stools. In those instances, the change of flora takes on a very slow course.

Blood.—The presence of either occult or fresh blood suggests the inflammatory or infectious processes going on in the intestinal tract. It may be due to hemorrhoids, fissure or ulcer in the lower part of colon in case fresh blood is found, and ulcer or cancer of the gastro-enteric tract in case of occult blood. Any infectious processes, such as typhoid, tuberculosis or diseases of a parasitic nature, often result in the presence of fresh blood. In such a case transformation takes place very slowly, and in the majority of cases will never occur until the interference is removed.

Pathogenic Parasites.—Pathogenic parasites are obstacles to the transformation of the flora. The changes that take place in the intestinal tract owing to their presence are not favorable for the growth and proliferation of *B. acidophilus*. In parasitic diseases, there is more or less a continual destruction of the intestinal wall; toxic substances are readily absorbed into the blood stream, and fermentative processes do not take place under such circumstances.

Summarizing these findings, we may say that the conditions favorable for the process of the transformation are a yellowish, soft, fluffy

11. Robinson, C. S.: J. Biol. Chem. **52**:445 (June) 1922.

stool with sour or non-odor, and an absence of mucus and blood as well as of parasites regardless of reaction. On the other hand, if the stool shows scybalic or diarrheal types, is dark brown, of putrid odor, with or without mucus, blood and parasites regardless of reaction, the putrefactive process is evident provided the bacteriologic examination presents the equivalent picture.

CONCLUSION

1. The bacteriologic examination advanced here is not for a detailed study of the intestinal bacteria, but to determine the general character of the flora.

2. Litmus milk, lactose broth, Veillon tube and dextrose agar plate, together with special milk culture to determine the spore-bearing type and microscopic examination, constitute the analysis of the intestinal flora.

3. Macroscopic and chemical examinations are necessary to corroborate the bacterial analysis, but the test should be made independently.

4. The classification of the flora is an arbitrary affair. The interpretation should be made on the summarized findings of all the examinations concerned.

DEFECTS OF MEMBRANOUS BONES, EXOPHTHALMOS AND DIABETES INSIPIDUS

REPORT OF A CASE WITH NECROPSY *

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OMAHA

In 1919, Christian,[1] under the title, "Defects in Membranous Bones, Exophthalmos and Diabetes Insipidus, an Unusual Syndrome of Dyspituitarism," reported a case presenting this syndrome and cited two similar cases previously described by Schüller.[2] Three other cases have since been reported by Hand[3] and one by Grosh and Stifel,[4] making seven cases in all reported to date. The following case was deemed worthy of a detailed report because of the unusually widespread osseous dissolution present, because of the rarity of the condition, and finally to record a complete postmortem study of this strange disease complex.

REPORT OF CASE

History.—C. J., a boy, aged nine years, came to us, Feb. 15, 1923, seeking relief from excessive thirst and frequent urination.

The father, mother, one sister and one brother were living and well. The mother had had no miscarriages. One brother died when five months old of cholera infantum.

The patient was born and raised in the Missouri Valley; his birth was at full term, the delivery being normal and his weight, 4.5 kg. He was bottle fed from birth; lime water was not added to the feedings. He had had chickenpox and scarlet fever in a mild form without complications. His growth and development were normal.

In December, 1922 (fourteen months before coming to us), the patient suffered a severe attack of measles which lasted for three weeks. No complications fol-

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1. Christian, H. A.: Contributions to Medical and Biological Research (Osler Festschrift), New York, Paul B. Hoeber, 1919, **1**:390-401. As Christian's excellent paper has formed and will continue to form the basis for studies of this baffling syndrome, it is suggested that for the sake of simplicity the name Christian's syndrome be used temporarily instead of the cumbersome defects in membranous bones, exophthalmos and diabetes insipidus.

2. Schüller, Artur: Ueber eigenartige Schadeldefekte in Jügendalter-Fortschritte der Roentgenstrahlen, 1915-1916, **23**:12.

3. Hand, Alfred: Defects of Membranous Bones, Exophthalmos and Polyuria in Childhood—Is It Dyspituitarism? Am. J. M. Sc. **162**:509 (Oct.) 1921.

4. Grosh, L. D., and Stifel, J. L.: Defects in Membranous Bones, Diabetes Insipidus and Exophthalmos with Report of a Case, Arch. Int. Med. **31**:76 (Jan.) 1923.

lowed save slight looseness of the teeth and soreness of the gums, which was thought to presage the eruption of permanent teeth. Convalescence, however, was protracted and he was left in a weakened condition from which he never recovered. Six months after his measles, excessive thirst and urination suddenly appeared, persisted for several days, then disappeared. At this time a small soft spot was noted on the right side of his head; little attention was accorded this softened spot as the mother thought it to be "Nature's way of accommodating a growing brain." About one year after the measles (three months before coming to us), the polydipsia and polyuria returned and persisted with increasing severity until he was drinking at every chance and passing from 6 to 12 liters of urine daily. His strength began to wane and his appetite to fail. On several occasions he became nauseated and vomited. He had no headache and no visual disturbances.

Physical Examination.—The patient was fairly well developed but emaciated. His color was sallow and dull and his facies that of an old man, but he was active, talkative and mentally keen, and apparently he felt well. The skin was

Fig. 1.—Patient, C. J., six weeks before death; flattening of left side of skull; bulging of left frontal and parotid regions; exophthalmos (more marked on left); prognathism; absence of teeth and facies of an old man.

coarse and dry. The chin was narrow and pointed; fulness was apparent in the left parotid region, and the frontal eminences were prominent. The skull was symmetrical without elevations. In the right parieto-occipital region was a soft, elastic depression about 4 cm. in diameter, the edges of which were irregular, firm and sharply chiseled. There was no tenderness except to deep pressure; the hair was abundant, dry, coarse and brown; the scalp was clean and without scars. There was no discharge from the ears. The eyes were prominent but there was neither lid-lag nor extrinsic muscle paralysis. There was slight nystagmus in all directions. There was no photophobia, diplopia or lacrimation. The conjunctivae were normal; the sclerae were white; the pupils were large, equal and regular, reacting normally to light and distance; the fundi were normal; the vision was normal. There was no gross deformity of the nose and no evidence of obstruction or discharge. The hearing was normal. The lips were of good color without herpes, fissures or ulcerations. The mucous membrane of the mouth was normal but there was marked gingivitis. The teeth were clean and sound

but loose. The tonsils were large and pale; liquid pus could be expressed from both. The pharynx was pale and covered with a slight amount of mucopurulent secretion. No pulsations were visible in the neck. The thyroid seemed small. Examination of the heart and lungs was negative. There was no evidence of an enlarged thymus. The abdomen was retracted and firm. There was no adenopathy. The hands were small and gracile. The genitalia were infantile. The deep and superficial reflexes were normal; there was no sensory disturbance or other evidence of peripheral or central nervous system involvement. The temperature was 36.6 degrees C., the pulse 90; the blood pressure was 90 systolic and 60 diastolic. The weight was 27.2 kg.

Laboratory and Special Findings.—Hemoglobin totaled 75 per cent. (Dare); erythrocytes, 4,120,000; leukocytes, 9,600, with normal spreads; the blood urea nitrogen was 19.5 mg. and the blood sugar 50 mg. per hundred cubic centimeters of blood; the blood Wassermann reaction was negative. The urine was water-pale and alkaline; the specific gravity was of 1.000; neither albumin, sugar reduction nor Bence-Jones albumose was found. Microscopic examination was negative. The cerebrospinal fluid was clear and came under normal pressure. The gold solution curve was 0000000000; globulin was slightly positive; there were four cells per cubic millimeter; the Wassermann test was negative. The spinal puncture had no effect on the water output. The basal metabolic rate was plus 8.

Roentgenograms taken at this time showed the skull (Fig. 2) to be normal in size and shape, with smooth and regular surfaces except at the vertex and in the frontal regions where the outer table alone was lacking. The thickness of the bones was otherwise normal. There appeared to be no diffuse involvement of bone, but throughout the upper three-fourths of the cranium were scattered numerous defects varying in size, roughly, from 2 to 40 mm. in diameter. The smaller areas were round or oval while the larger ones were quite irregular. The distribution of the lesions was asymmetrical. The superior orbital plates were involved. Both maxillae showed spotted areas of bone absorption similar to those in the skull. The sella turcica appeared normal in size and shape, its floor smooth and regular. It measured 12 by 8 mm. The anterior and posterior clinoid processes were 5 mm. apart. The pelvic bones showed lesions similar to those in the skull. In the left ilium was an irregular area 15 by 20 mm. The right ilium, as well as both ischii, showed smaller scattered areas of rarefaction (Fig. 3). The right femur showed beginning lesions only in the upper part of the shaft, but in the upper third of the shaft of the left femur and in the neck there were definite areas of rarefaction. The epiphyses on the heads and greater trochanters were ununited. Partial collapse of the body of the fourth lumbar vertebra was evident. At this time a tentative diagnosis of multiple myeloma was made from the roentgenologic findings, even in the absence of Bence-Jones albumose and of all evidence of tumor.

Interval History.—Subcutaneous injections of pituitary extract accomplished a reduction of the urine output of from 4 to 8 liters a day. The specific gravity

Explanation of Plate 1

Fig. 2.—Skull, Feb. 15, 1923, nine months after the first appearance of symptoms.

Fig. 3.—Pelvis, Feb. 15, 1923, showing definite bone defects in ilia, ischia and femur.

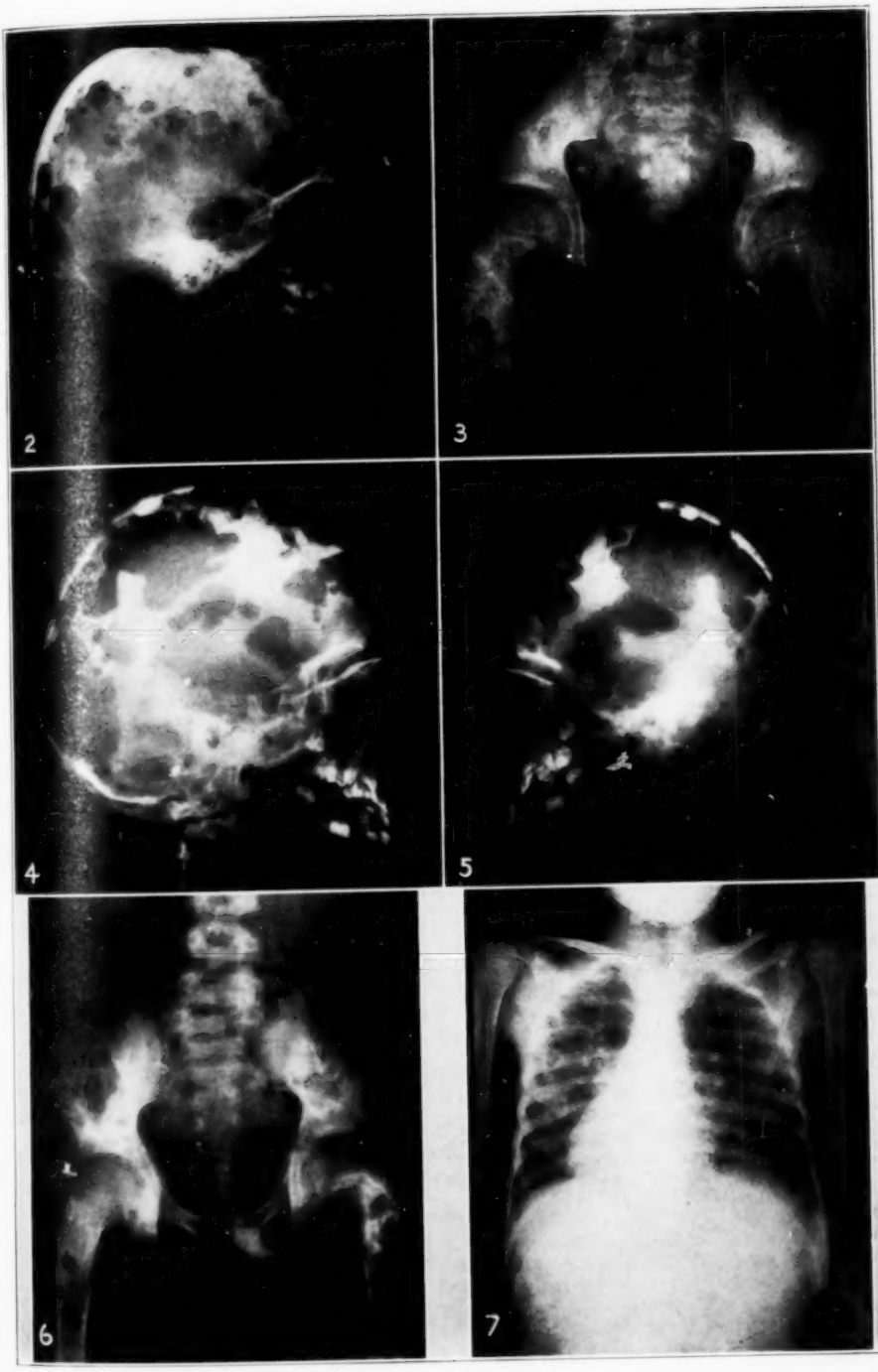
Fig. 4.—Skull, Feb. 14, 1924, one year later than Figure 2.

Fig. 5.—Skull, June 21, 1924; marked increase in bone destruction, which had taken place in four months.

Fig. 6.—Pelvis, June 21, 1924; increase in bone destruction.

Fig. 7.—Chest showing bone defects in humeri, claviculi and ribs. The fine mottling of an interstitial pulmonitis that was characteristic in stereoscopic plates can be detected.

PLATE 1



varied from 1.000 to 1.010. After six months of hypodermic pituitary extract treatment, epistaxis set in; the patient's appetite failed, and each injection of pituitary extract was followed by pain in the epigastrium and precordial distress. The pituitary extract was discontinued. The distressing abdominal symptoms were relieved but the polyuria returned with increasing severity. The patient was given 45 grains (2.9 gm.) of calcium lactate daily, a sufficient quantity of lime water in milk, and ground egg-shells in capsules (a home suggestion). The taking of lime salts apparently affected the boy's sense of well-being because when they were stopped on several occasions he remarked that he did not feel so well. Thyroid therapy was of no apparent benefit. A nasal spray of pituitary extract controlled the polyuria quite satisfactorily. About eight months after the first examination exophthalmos was already marked and lacrimation troublesome. He suffered some from lumbar backache and slight pain in the left hip at times, but he had always been about and felt quite well. Except for a troublesome cough with a mucopurulent sputum, which was repeatedly negative for tubercle bacilli, and an ominously increasing dyspnea, the patient's general condition remained surprisingly good.

The following notes were taken from an examination record made June 21, 1924, about two years after the onset of the disease, sixteen months after our first observation and six weeks prior to the patient's death. The patient walked with a marked limp, listing forward and to the left in the manner of a congenital dislocation of the hip. Pallor was pronounced; the cheeks were sunken (there

Calcium Determination

Urine	Amount	Method	Calcium
7/ 9/24	2,600 c.c. (24 hours)	McCrudden	128 mg.
	2,660 c.c. (24 hours)	Kramer and Tisdall	152 mg.
7/10/24	1,400 c.c. (12 hours)	McCrudden	8 mg.
	1,400 c.c. (12 hours)	Kramer and Tisdall	36 mg.
7/15/24	3,440 c.c. (24 hours)	McCrudden	7.3 mg.
Blood Serum			
7/15/24	13.6 mg. per 100 c.c.		

had been a loss of 2.7 kg. in body weight); the eyes were prominent, and the palpebral fissures widened (Fig. 1). Exophthalmos was marked; lid-lag was present, and the visual fields were normal. Fulness in the left parotid region and bulging of the forehead between the eyes was striking. The entire skull was soft and doughy with only a coarse irregular framework of supporting bony ridges. Straining or coughing caused the soft areas to bulge. The gingivitis was severe and the teeth were held only by the soft investing tissue, as the alveolar processes had been absorbed. There was some mucopurulent material on the posterior pharyngeal walls and pus could be expressed from the tonsils and gums. There was moderate general adenopathy, which had developed during the last year, but the spleen was not enlarged. The lungs were hyperresonant to percussion with numerous small and large dry râles and prolonged expiration. The spine had become bent forward in the lumbodorsal region with an even curve. There were no visible or palpable bony deformities of the extremities or spine.

The laboratory findings at this time were: hemoglobin, 60 per cent.; erythrocytes, 3,800,000; leukocytes, 10,200, with polymorphonuclears, 71 per cent.; small lymphocytes, 20 per cent.; large lymphocytes, 18 per cent., and eosinophils, 1 per cent. The urine was clear and alkaline in reaction with a specific gravity of 1.000 without albumin, sugar or Bence-Jones albumose. Microscopic examination was negative. The calcium determinations are given in the accompanying table.[5]

5. The methods used were those of McCrudden, F. H.: J. Biol Chem. **7**:83, 1910, and of Kramer, B., and Tisdall, F. T.: Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921. It is to be regretted that hospitalization was not permitted for complete metabolic studies as a satisfactory solution of this syndrome will probably not be obtained without more complete knowledge of its metabolism.

A roentgenologic study of the entire skeleton at this time revealed the following:

The skull truly merited the term geographic (Fig. 5). On the left side of the skull in the rear portion of the left frontal bone there was an irregular area of bone estimated at 30 mm. long and 20 mm. wide, and an irregular area in the parietal bone 20 by 15 mm. Except for these islets of bone the entire fronto-parietal region was gone. The occipital bone was largely free from destruction except in the region of the lambdoid suture. On the right side easily half the skull was gone and on the left side fully three-fourths. There was a definite dissolution of continuity, or *faulting* of the frontal bone, measuring fully 4 mm. The sella turcica, except for a small spot in the anterior wall, was without evidence of erosion and was normal in shape and contour except that the posterior clinoid processes were quite thick, set well back and erect. The sum total of bone loss in the skull had practically doubled in the last five months. In one and one-half years it had increased at least tenfold (Figs. 2, 4 and 5). Decalcification was extensive in both jaws.

The bones in both feet and legs were normal except that the shafts of the tibiae showed a moderate periostitis. The bones of the hands and forearms were normal.

The ilia showed many and extensive areas of decalcification (Fig. 6). The upper end of the shaft and the neck of the left femur showed one decalcified area about 2 cm. in diameter. The right ischium showed several areas of decalcification and also some excess of bone production. Practically all the ribs showed areas of decalcification. The shaft of the right humerus throughout its middle third showed numerous small areas and the head of the left beginning spots of decalcification (Fig. 7). The cervical vertebrae showed considerable decalcification which was especially noticeable in the sixth and seventh. There were bone defects in both scapulae. The clavicles appeared normal.

Roentgenograms of the chest (Fig. 7) revealed the diffuse increase in density characteristic of chronic interstitial pulmonitis.

As death approached the cough and dyspnea became more and more troublesome. Attacks of nocturnal dyspnea with tachycardia recurred with increasing frequency. Exitus came quite rapidly from cardiac failure, attributed to impaired circulation incident to extensive pulmonary fibrosis.

CLINICAL COMMENT

It is obvious that clinical interest in this unusual syndrome must center about (1) the bone destruction and the mechanical disturbance that may arise therefrom; (2) the sella turcica, because of prevalent conception of the rôle of the hypophysis in skeletal growth and diabetes insipidus; (3) the pathogenesis of diabetes insipidus, and (4) any etiologic inferences the behavior of the disease may suggest.

Defects in Bones.—In surveying the cases reported, "defects in membranous bones" loom large. The defects in the cranial bones in our case made a startling picture—a head of jelly with only a few struts and girders of bone to support it. The *faulting* of the frontal bone with its orbital plates fully explained the exophthalmos. After the patient had been up and about, the exophthalmos was relatively equal in both eyes; after he had lain for an hour or two on either side the protrusion of the "down" eye would increase markedly and the "up" eye would recede. Physiologic disturbances in other intracranial structures, such as the hypothalamus, might be logically postulated on a

mechanical basis alone, or through involvement of adjacent tissues by the same processes that were accomplishing bone destruction. The peculiar gait and "listing" of our patient was accounted for by the destruction of the body of the fourth lumbar vertebra.

Sella Turcica.—Changes in the sella have not been an outstanding feature in reported cases:

> The sella turcica was somewhat enlarged and slightly flattened and in the stereoscopic view it looks as if there is a slight defect in the base of the skull very close to, if not continuous with, the sella turcica (Christian).
>
> The sella turcica is markedly changed, only the dorsum sella is present, the anterior part of the floor of the sella is greatly deepened (Schüller's Case 2).[6]

In only one of Hand's cases was there a roentgenogram; this showed "the sella turcica to be uninvolved in the bone change." In Grosh and Stifel's case, they stated that the bones forming the bridge of the nose were not involved nor the sella turcica, which was normal. In our case stereoscopic roentgenograms revealed no changes in the size or contour of the the sella such as might reasonably denote abnormalities in the hypophysis, only a small defect in the floor of the sella being suspected. Out of five cases in which mention of the sella was made only one case showed definite sellar changes, a high percentage of normality if we are to assume a pituitary origin for the syndrome. Furthermore, because the hypophysis seems to have something to do with the laying down of bone in skeletal growth there is no evidence that by a reverse process it may cause wholesale destruction of disseminated areas of normally built bone.

Diabetes Insipidus.—While diabetes insipidus has been commonly found in lesions of the pituitary gland, two views prevail as to its pathogenesis. An older and generally accepted view is that it is due to pituitary disease. Rowntree[7] was unable to find in the literature any case of diabetes insipidus in which the necropsy failed to show changes in the pituitary gland. Motzfeldt[8] concurs. Engelbach and Tierney[9] also assume a deficiency disease and call attention to the "strange tendency to exclude pituitary disorder in the absence of typical sellar erosions or deformities." Furthermore, that posterior lobe extract or pituitary extract is the only agent known to control the polyuria is interpreted in

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6. It would seem that for the sake of clarity Schüller's Case 1 should not be included in this syndrome. This patient did not have diabetes insipidus but dystrophia adiposo genitalis; the defect in the cranial bones was largely confined to one side (the left). Schüller's assumption was a tumor at the base of the brain ("other changes suggested pressure"), either an angioma of the dura or of the skull.

7. Rowntree, L. G.: Oxford Med. **4**:185, 1921.

8. Motzfeldt, K.: Endocrinology **2**:94, 1918.

9. Engelbach, W., and Tierney, J. L.: Pituitary Polyuria, Internat. Clinics **4**:123, 1920.

the light of substitution therapy. On the other hand there is much experimental evidence for the other view, that diabetes insipidus is of extrahypophyseal, or basilar, origin. Sajous [10] gives an excellent exposition of this theory. The argument that diabetes insipidus is a pituitary deficiency disease because the polyuria is controlled by pituitary extract is met by the argument that no one would assume that asthma is a suprarenal deficiency disease because it may be controlled by epinephrin. Furthermore, there is much evidence, largely experimental, in favor of an extrahypophyseal origin. Camus [11] and Roussy [12] punctured through the sphenoid bone with a heated drill without injuring the hypophysis, the region known to anatomists as the hypothalamus, and thus induced permanent polyuria. They also produced polyuria in a dog without polyuria from which the hypophysis had previously been removed, demonstrating that the polyuria did not depend on the hypophysis. Bailey and Bremer [13] repeated the experiments and confirmed the results of Camus and Roussy, using the Paulesco-Cushing method of lateral approach. They succeeded in producing polyuria in thirteen out of thirteen dogs by injury of the hypothalamic region without trauma to the hypophysis. The results of numerous tests carried out on these dogs justified to them "the conclusion that the persistent polyuria provoked in this manner (by lesions of the para-infundibular region of the hypothalamus) has all the characteristics of diabetes insipidus." This experimental diabetes persisted after denervation of the kidney and therefore could not be atttributed to nervous or vasomotor disturbances. Hanchett [14] was able to produce polyuria in only one instance in nine dogs by stimulation of the anterior and posterior lobes of the hypophysis with a hot rod. On the other hand he was able to induce polyuria regularly by traction on the stalk. Hanchett concludes:

> Experimental lesions of the hypophysis similar to those producing negligible excretory changes, when associated with traction on its attachment to the floor of the third ventricle, uniformly produced polyuria. The degree of polyuria was roughly in proportion to the amount of traction.

Curtis [15] confirmed the experimental results of Camus and Roussy, Hanchett, and Bailey and Bremer in that diabetes insipidus is essentially of hypothalamic origin; he regards experimental diabetes insipidus

10. Sajous, C. E. D.: Am. J. M. Sc. **167**:679-696 (May) 1924.
11. Camus, J., and Roussy, G.: Compt. rend. Soc. de biol. **75**:483, 1913.
12. Camus, J., and Roussy, G.: Endocrinology **4**:507 (Oct.-Dec.) 1920.
13. Bailey, Percival; and Bremer, Frederic: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773 (Dec.) 1921.
14. Hanchett, M.: Experimental Polyuria, Am. J. M. Sc. **163**:685 (May) 1922.
15. Curtis, G. M.: The Production of Experimental Diabetes Insipidus, Arch. Int. Med. **34**:801 (Dec.) 1924.

as essentially a "hypothalamic thirst phenomenon." In the absence of definite sella changes and in the light of recent experimental results, we were not justified in assuming clinically the existence of hypophyseal disease in our patient.

Etiologic Inferences.—The close relationship of antecedent infections to the disease is worthy of notice. Christian's patient had mumps four months before entrance to the hospital, and loosening of the teeth and swelling of the gums six months before. In Schüller's Case 2, the patient had whooping cough six months prior to the sudden development of left sided exophthalmos. Hand's first case was admittedly infectious and was diagnosed tuberculosis, although the necropsy failed to demonstrate characteristic tuberculous lesions. In Hand's Case 2, recession of the gums with the gradual loss of teeth began from five to six months after scarlet fever. At the same time a soft spot was noted in the head. Twenty months after the scarlet fever, diabetes insipidus appeared.[16] In Grosh and Stifel's case polyuria developed seven weeks after drainage of the left mastoid; preceding this for some time the patient had had a discharging ear. Our patient never recovered fully from a severe attack of measles followed by sore gums and loosening of the teeth, which preceded the first attack of polyuria and the first softening of the bone by six months. In only three cases were leukocyte counts made. In Christian's case, the leukocyte count ranged from 6,600 to 12,600 with an occasional rise to 14,100, 15,600 and 20,100, the differential on admission showing polymorphonuclears 30 per cent., lymphocytes 45 per cent., large mononuclears 23 per cent. and eosinophils 2 per cent. In Grosh and Stifel's case, one count of 8,000 leukocytes with normal spreads is recorded. In our case, three counts varied from 9,600 to 10,200, with polymorphonuclears 71 per cent., small mononuclears 20 per cent., large mononuclears 18 per cent. and eosinophils 1 per cent. on one count. The temperature was not noted in any of the other cases, except in Hand's first case, in which temperatures of 102.2, 99 and 105 degrees were noted. Occasional unaccountable rises of temperature to 101 degrees were noted in our patient. The existence of widespread infection was further supported by the signs of diffuse pulmonary infection with the clinical and roentgenologic findings of a chronic interstitial pulmonitis, infected tonsils, gingivitis, postnasal discharge and the later development of a general adenopathy.

NECROPSY

The body was that of an embalmed white boy, appearing older than the given age of 11 years. The development was fairly normal; the skin was pale and nutrition poor.

16. In Hand's Case 3, which was incompletely studied, there was no polyuria, but the patient did have characteristic defects in the membranous bones.

In the head, the most noticeable feature was a marked bilateral exophthalmos, more pronounced in the left eye, which was distinctly lower than the right (estimated 5 mm.). The nose was small and the bridge sunken. Many teeth were absent. The contour of the cranial vault was distinctly asymmetrical, with a soft flattened forehead and soft, pliable parietal regions. Palpation revealed an extensive bone deficiency—a membranous cranium. A narrow, irregular, sharply delimited bridge of bone extended diagonally across the vault from the right external orbital process to the left mastoid. In the frontal region, the membranous cranium was limited by a sharp border with two processes jutting upward about 3 cm. from each supra-orbital ridge. In the midline, the bone deficiency extended to and included the nasal bones. In the left temporal region, the membranous cranium reached to the level of the zygomatic arch, while in the right temporal region, the bone border was at the middle of the squamous part of the temporal bone. Posteriorly, the bone deficiency was limited by the superior occipital line, except for a projecting spine of bone about 2 cm. long in the midline. The scalp and aponeurosis stripped easily from the bone and the membranous cranium beneath. In the center of the largest membranous areas, there was slight adherence by yellowish fibrous tissue. The underlying membranous cranium was opaque and had a mottled angulated appearance. The bone edges were abrupt and sharp.

The membranous cranium, which included a rather firmly adherent dura mater, was cut easily with knife and scissors. The subdural space was normally free. The inner surface of the dura beneath the membranous cranium was mottled by a dull, yellowish tissue, which took a scharlach r fat stain. Microscopic section through this region showed a lining layer of large oval cells, with sharp borders, with clear, slightly granular cytoplasm, and small compact centrally placed nuclei. The cytoplasm contained a variable amount of lipoid material in finely divided form. The cranial membrane that this fatty layer lined consisted of typical dense white fibrous tissue, with no evident lines of cleavage between the dura proper, the endosteum, the absorbed cranial bone and the periosteum. The dura of the falx cerebri and that beneath the intact cranial bone had a normal smooth, white, glistening appearance and stripped easily, revealing a gray, translucent tissue fitting closely into the groove between the two tables at the bone margin. Microscopic sections of this tissue at the bone edge showed a highly cellular tissue composed chiefly of large cells with eosinophilic cytoplasm and large reticular nuclei. In many places, particularly at the bone border, these cells appeared to have fused to form large multinuclear, foreign body giant cells (Fig. 8, giant cells at bone border). The nuclei in some were arranged peripherally in a semicircular manner, but the majority were centrally located, the nuclei numbering from a few to twenty or more. The remaining cells of this soft tissue consisted of lymphocytes, plasma cells and polymorphonuclear leukocytes and eosinophilic cells. Quite dense infiltrations of each of these cell types could be found in different regions. There was a gradual narrowing and complete fibrosis of this tissue from 5 to 10 mm. from the bone edge, where it joined the dura to form the membranous cranium (Fig. 9, transition from cranial bone to membrane). The larger areas of bone by transmitted light showed round or oval decalcified areas of variable size, bounded by the same grayish cellular tissue at the border. The dura and periosteum were adherent over these areas. Other darkened areas were seen in the bone where the external and internal tables were intact and the periosteum not firmly adherent. Microscopic section of these showed a beginning cellular proliferation and infiltration in the diploetic spaces similar to those described above.

The exposed convex surface of the cerebral hemispheres appeared entirely normal in size, color and conformation. There was no involvement or thickening of the pia-arachnoid. Elevation of the frontal lobes of the brain revealed an enlarged, yellowish infundibular stalk, measuring from 2 to 3 mm. in diameter. This yellowish involvement of the infundibulum extended as a

bulbous enlargement into the tuber cinereum (Fig. 10, basilar view of tuber cinereum) and was distinctly outlined in the median sagittal section from the optic chiasma in front and the gray brain substance above (Fig. 11, median sagittal view of tuber cinereum). Serial sections were made of the tuber cinereum and adjacent structures (Fig. 12, sagittal section of tuber cinereum). The region of the pathologic condition appeared as a darker stained area 3 mm. in diameter, with a somewhat indistinct upper border, which was histologically similar to the soft tissue at the cranial bone edge. At the lower edge of the infundibulum, several normal glandular acini were seen surrounded by a millimeter or two of tissue composed chiefly of large cells with abundant pale eosinophilic cytoplasm and fairly large reticular nuclei. A few cells appeared to have fused to form multinuclear giant cells. There was a moderate infiltration with mononuclear cells, but with very few polymorphonuclear leukocytes. A process of fibrosis appeared under way, the cells alining themselves in parallels and whorls and having the appearance of fibroblasts. There were very few blood vessels. The microscopic picture farther up into the tuber cinereum showed a central strand of dense white fibrous tissue, continuous with a very dense fibrosis comprising the entire area of junction with the nervous tissue (Fig. 13, dense fibrosis of tuber cinereum). Where this pathologic condition extended into the brain tissue, there was a marked perivascular mononuclear cell infiltration. This perivascular infiltration extended a short distance into the nervous tissue beyond the fibrosis (Fig. 14, perivascular infiltration in nervous tissue). Bordering on the dense fibrous tissue of the tuber cinereum was the characteristic eosinophilic cellular tissue described in the infundibulum. This extended several millimeters upward along the posterior border of the tuber cinereum, apparantly as a pial perivascular infiltration, to the same level as the perivascular infiltration in the nervous tissue. Multinuclear giant cell formation was quite prominent in this region (Fig. 15, multinuclear giant cells in the tuber cinereum). A focus of dense small mononuclear cell infiltration was present at the base of the fibrous one (Fig. 16, focus of lymphocytic infiltration in tuber cinereum). There was a sharp line of separation anteriorly between the optic chiasm and the cellular zone. A slight perivascular cell infiltration extended into the upper and lateral part of the chiasm.

The hypophysis with its dural envelop was removed intact. It was of normal size and reddish. The infundibulum at its junction with the gland was of normal size and appearance, measuring from 1 to 2 mm. in diameter. A gross sagittal section of the pituitary gland showed normal anterior and posterior lobes. Serial sagittal sections of the gland and dura, including the infundibulum, were made. Microscopically, the anterior lobe showed the normal elements of large, brightly stained pink cells (eosinophilic), large, darkly stained blue cells (basophilic) and a few small, pale blue cells (neutrophilic or chromophobic) arranged in cords and separated by vascular stroma. The basophilic cell predominated in the anterior region where there were only scattered eosinophilic cords. The eosinophilic cells predominated in the central region

Explanation of Plate 2

Fig. 8.—Foreign body giant cells, polymorphonuclear leukocytes and plasma cells in tissue obtained from seat of active bone destruction.

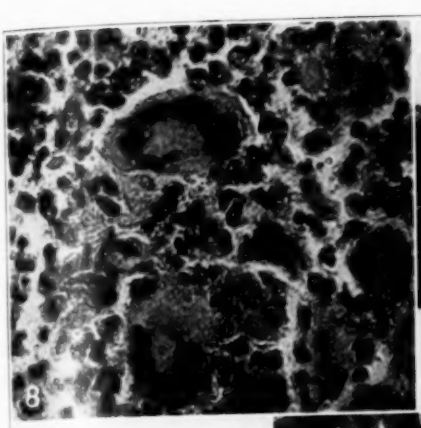
Fig. 9.—Normal bone showing area of active bone destruction with fusion of periosteum, endosteum and dura to form the membranous cranium.

Fig. 10.—Basilar view of tube cinereum with yellowish bulbous enlargement.

Fig. 11.—Median sagittal view of tuber cinereum.

Fig. 12.—Sagittal section of tuber cinereum showing area of active inflammation.

Fig. 13.—Dense fibrosis in tuber cinereum.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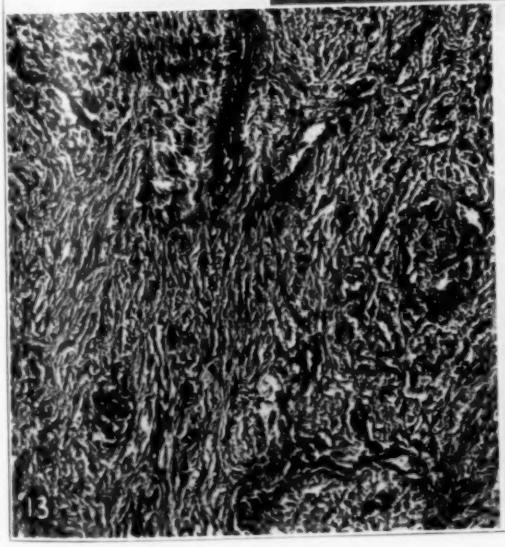
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and all three types of cells appeared indiscriminately mixed in the posterior region, with possibly a predominance of neutrophils (chromophobes). The pars intermedia was rather poorly defined but was identified by its position and by its fibrous stroma, indefinite cell elements and a few alveoli containing colloid. The pars posterior or pars nervosa was not entirely normal. The most evident pathologic condition was a slight infiltration of polymorphonuclear neutrophilic and eosinophilic leukocytes without increase of fibrous tissue. Small scattered foci of degenerated cells and peripheral foci of basophilic mononuclear cells resembling lymphoid follicles were found. The pathology was interpreted as a subacute degenerative and inflammatory process of relatively recent origin. The base of the infundibulum showed a considerable dense, white fibrous stroma with an extension into it of the normal cellular elements of the pars posterior and of the glandular elements of the pars anterior. Surrounding this was a tissue composed chiefly of faintly stained large eosinophilic cells, fusing in places to form multinuclear giant cells, and moderately infiltrated with smaller mononuclear cells. This tissue, which had embedded in it a few glandular cords and alveoli, was thickest on the anterior surface of the infundibulum and could be traced a short distance into the superior portion of the pars anterior of the pituitary gland. The dura surrounding the pituitary gland appeared intact as a dense, white, fibrous tissue, although anteriorly there was attached to its outer surface a cellular tissue composed of pale eosinophilic cells and a varying amount of fibrous stroma, infiltrated with mononuclear, polymorphonuclear and eosinophilic cells. This tissue evidently arose from an adjacent decalcified area of bone in the right anterior wall of the pituitary fossa. It did not appear to extend through the dura at any place. Posteriorly, the dura surrounded a rather narrow extension of the pars posterior, the center of which showed some necrosis. Above the pars posterior there was quite a thick fibrous layer which was continuous with the fibrous septum of the pars intermedia and also with the central fibrous strand of the infundibulum.

The pituitary fossa appeared of normal size and shape except that the anterior clinoid processes seemed to be depressed, owing to a dropping of the lesser wings of the sphenoid bone and the superior orbital plates. The following measurements of the pituitary fossa were taken: between anterior clinoids, 23 mm.; anterior-posterior, 12 mm.; width of dorsum sellae, 17 mm.; thickness of dorsum sellae, 4 mm.; depth of pituitary fossa, 9 mm.; width of base of pituitary fossa, 11 mm., and anterior-posterior of fossa, 10 mm. In the right anterior and inferior region of the pituitary fossa was a decalcified area of bone, 5 mm. wide and 8 mm. long, which extended forward under the lesser wing of the sphenoid (Fig. 17, pituitary fossa showing erosion in the floor). The floor of the skull showed extensive bone defects in the anterior and middle fossae. Bone destruction was so distributed in the anterior fossa that the entire mesial borders of the superior orbital plates were freed and could be easily depressed with the finger. The left orbital plate was loosened by extensive bone absorption which had involved the temporal plate of the frontal bone, the greater wing of the sphenoid, the squamous portion of the temporal bone

Explanation of Plate 3

Fig. 14.—Perivascular infiltration in brain tissue adjacent to tuber cinereum.

Fig. 15.—Multinuclear giant cells in tuber cinereum of same type as found at bone margin.

Fig. 16.—Focus of lymphocytic infiltration in tuber cinereum.

Fig. 17.—Bone defects in base of skull, showing faulting of orbital plates.

Fig. 18.—Proximal end of left femur showing bone defects.

Fig. 19.—Interstitial fibrosis of lung; the same general process as found in the bone margin and tuber cinereum.

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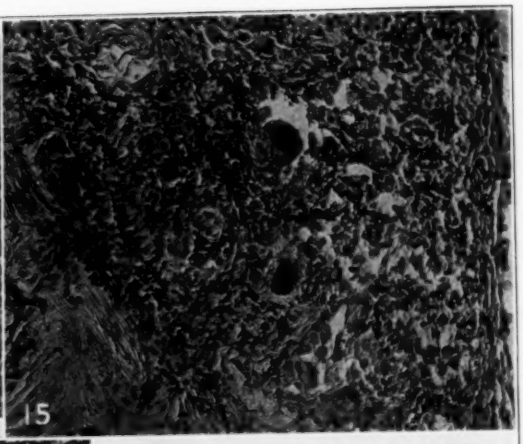
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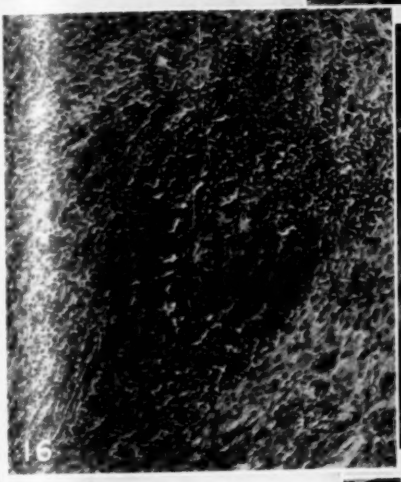
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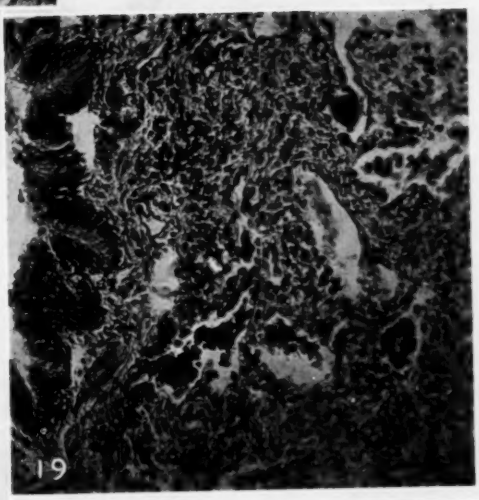
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and the suture line between the orbital plate and the lesser wing of the sphenoid. Some supporting bone remained on the right side. The loosening and depression of the superior orbital plates could easily account for the exophthalmos.

The greater wings of the sphenoid bone were extensively decalcified in an irregular manner. The larger defects were filled with a mixture of dense yellowish-white fibrous tissue with grayish cellular tissue at the bone margins. Sections of this tissue showed the same cellular characteristics as described in the cranial bones of the vault. Mononuclear cells predominated, with scattered giant cells, and polymorphonuclear and eosinophilic cell infiltrations. The white fibrous tissue showed dense collagen fibrils and a few small nuclei. The squamous portions of both temporal bones were decalcified in a similar manner; there was no involvement of the petrous portions, mastoids, or middle ear cavities. The nuchal portion of the occipital bone was intact but most of the cerebral portion was decalcified. The sphenoid sinus was involved in the destructive process affecting the anterior cerebral fossa and was filled by dense white fibrous tissue. The ethmoid cells were likewise obliterated by tissue growth.

The proximal extremity of the left femur was removed and examined. A round decalcified area, 1 cm. in diameter, was found on the lateral surface just below the greater trochanter (Fig. 18, proximal extremity of the left femur). There was no change in contour lines, no unusual adherence of the periosteum, and the bone edge surrounding the area was quite sharp. The same process involved the cancellous bone between the trochanters. The cut surface showed a fairly firm, grayish white tissue. Sections of this tissue, including the bone border of the lateral cortical defect, showed the same process of variable cellular infiltration, multinuclear giant cell formation and transformation from loose to firm fibrous tissue described elsewhere.

The thyroid gland was of normal size, appearance and histologic structure. Two parathyroid glands were identified in the posterior capsule of the thyroid as small grayish red oval bodies about 2 mm. long; they were histologically normal.

The pleural cavities were free from adhesions. The lungs were firm and pale from formaldehyd fixation. No nodules were present. Microscopically, there was found an extreme interstitial fibrosis, the alveolar walls being thickened to a degree which almost obliterated the normal lung architecture (Fig. 19, interstitial fibrosis of lung). There was a moderate mononuclear cell infiltration in this tissue and numerous small blood vessels. A few polymorphonuclear cells were present. Some of these thickened septums were covered with a single layer of cuboidal epithelium. In places this appeared desquamated and formed confluent masses of cells. The bronchioles were enlarged and lined with a hyperplastic layer of columnar epithelium. There was no cellular material in the lumina. The heart was slightly enlarged; the right ventricular wall particularly was thickened. The valves were normal. Microscopically, the myocardial fibers were well defined, slightly granular, closely approximated and not fragmented. There was no infiltration. The aorta and coronary vessels were normal.

When the abdomen was examined, the peritoneum was smooth and glistening. The liver was about 5 cm. below the costal margin in the midclavicular line, dark red and enlarged. Microscopically, the liver cords were everywhere well defined, the cells showing little granular degeneration or vacuolation. A few cords contained bile pigment. The liver sinuses were dilated and contained an occasional polymorphonuclear leukocyte. The portal areas showed no fibrosis. The gallbladder was normal and the bile ducts patent. The stomach was contracted, pale and showed no tumor masses or ulcers. Grossly and microscopically, the gastro-intestinal tract was practically normal. The pancreas was grossly and microscopically normal. The spleen was slightly

enlarged, firm and dark red. Microscopically, there was a marked engorgement of the sinuses with red blood cells and a considerable number of cells packed with hemosiderin pigment. The septums were not thickened. The splenic nodules were quite prominent as basophilic cellular areas as contrasted with the eosinophilic pulp. The central arteries were normal. The kidneys were distinctly enlarged and slightly lobulated. Gross section showed a normally striated and delimited cortex, 7 mm. in width. Microscopic sections showed numerous large normal glomeruli. The convoluted tubules had large cells with abundant eosinophilic granular cytoplasm, brush border and slight elevation into the lumen. The loops of Henle could be characteristically differentiated into descending and ascending limbs. There was no interstitial tissue increase or infiltration. The pelvis of the kidney and the ureters were normal. The bladder wall was markedly thickened from muscle hypertrophy. The mucosa was pale and smooth. The suprarenals were of normal size, the cortex yellow, the medulla intact and not thickened. They were histologically normal.

The pathologic diagnosis was exophthalmos; decalcification of the bones; fibrosis of the tuber cinereum; slight subacute inflammation of the pars posterior of the pituitary gland; chronic interstitial fibrosis of the lungs; hypertrophy of the heart; chronic passive congestion of the liver and the spleen; hypertrophy of the kidneys, and hypertrophy of the bladder.

A necropsy of a case of defects in membranous bones, exophthalmos and diabetes insipidus, while giving highly instructive and suggestive findings, fails to fix beyond all peradventure the nature and cause of the disease. Histopathologic studies point to an inflammatory rather than to a degenerative or a primary metabolic process. The absence of any material pathologic condition in the anterior lobe of the hypophysis excludes it as a factor in the bony defects. The relatively negligible changes found in the pars posterior and the fact that their apparent origin was more recent than those changes found in the tuber cinereum, in the bones, and in the lungs eliminates the pars posterior as an important factor in pathogenesis. If the hypophysis were to be held in any way responsible for such widespread, bizarre disease processes one would expect more than the rather negligible pathologic changes found in the gland proper. The other ductless glands were found to be normal.[17] The preponderance of evidence is against an endocrinologic origin for the syndrome unless perchance one wishes to consider the tuber cinereum an endocrine, and to attribute to a diseased tuber unlimited powers of bone destruction. The changes in the stalk appeared of more recent origin, lessening the possibility of its participation in the causation of the syndrome. That the lesion in the tuber cinereum was the probable cause of the diabetes insipidus, however, is supported by the results obtained by Camus and Roussy, Hachett, Bailey and Bremer, and Curtis in their work on experimental polyuria in dogs. The lesions in the tuber cinereum were of the same character and apparent maturity as the lesions in the bone and in the lungs, which suggests that these

17. While the testes were examined at necropsy and were pronounced grossly normal, they were inadvertently not included in the material saved for histologic studies.

lesions were produced by the same agent at about the same time. The inflammatory character of the histopathologic condition, supported by numerous facts brought out in the clinical study, viz., fever, onset subsequent to measles, secondary anemia, chronic interstitial pulmonitis, marked gingivitis, markedly infected tonsils, etc., points to an infectious origin. In other words, an organism with bone-lytic properties or with the capacity to induce tissues to produce bone lysis would seem a reasonable etiologic explanation for the disease.[18] On account of the absence of tumor, and on account of numerous differences in clinical behavior myelomatosis was excluded, although the histologic structure of some of the material was very similar to that described by Berkheiser as multiple myelomas in children.[19] Furthermore, the infectious theory of the origin of multiple myelomas is as fitting as any. If the infectious hypothesis is true, we may expect to find cases without diabetes insipidus (absence of hypothalamic involvement?) and with other symptoms depending on involvement of structures not materially affected in our case. Clinically and pathologically considered, destruction of membranous bones was the paramount disease process in our case, exophthalmos a mechanical effect, and diabetes insipidus probably a result of associated involvement of the tuber cinereum.

SUMMARY

In a case of defects in membranous bones, exophthalmos and diabetes insipidus studied clinically and pathologically, dyspituitarism as a cause for the syndrome was excluded by the absence of material pathologic changes in the hypophysis. Pathologic support was given to current work on experimental polyuria which puts the lesion of diabetes insipidus in the hypothalamus. From clinical behavior and from pathologic findings an infectious etiology seemed more likely than a primary metabolic (endocrinologic) disturbance.

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18. It was suggested that the lung condition by causing tissue asphyxia might have induced calcium absorption and have thus played a part in the bone destruction. One of us (A. D. D.) has seen three cases at necropsy with fully as marked lung findings of a similar character in which there were no skeletal changes.

19. Berkheiser, E. J.: Multiple Myelomas in Children, Arch. Surg. **8**:853-881 (May) 1924.

LIPEMIA AND THE RETICULO-ENDOTHELIAL APPARATUS *

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The old blood letters were well aware that under certain pathologic conditions, notably severe diabetes mellitus, the blood may contain an excess of fat so great that, on being left to stand, a thick, creamy layer separates at the top, and that at necropsy creamy masses are found above the clots in the cavities of the heart and in the large vessels throughout the body. It was thought that the presence of such large amounts of fat in the blood stream must of necessity mechanically impede the circulation and perhaps give rise to fat emboli. Best known and most persistent of these hypotheses was the one that attributed diabetic coma to fat embolism of the brain. The untenability of this view was shown by the fact that diabetic coma often occurs in the absence of any considerable lipemia and vice versa. Though the quantity of fat in the blood may be enormous, even surpassing 25 per cent. by weight, fat emboli do not occur because of the exceedingly fine state of dispersion of the emulsified fat, in contradistinction to the large drops that enter the circulation following trauma to the bone marrow. Any anatomic findings encountered in a case of lipemia, therefore, are not to be attributed to fat embolism. Nor is there any evidence that the large amount of fat so alters the viscosity or other physical properties of the blood as to increase mechanically the work of the heart.

The first to note any morphologic changes in the organs due to lipemia, so far as we can ascertain, was the Scotch clinician Coats.[1] Describing the postmortem findings in two diabetic patients who died in coma with lipemia, he wrote: "The spleen had an extraordinary pale color suggestive of salmon roe;" and, "The appearance of the spleen in the first case was very peculiar and was such as I have never before observed myself or seen described. On microscopic examination it was seen that there were large cells abundantly present strikingly demarcated by being filled with fine granules, some of which were fatty. The splenic tissues was in great part made up of these large cells."

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* From the medical division of the Montefiore Hospital.

1. Coats, Joseph: On Two Cases of Diabetes Associated with Lipemia, Glasgow M. J. **32**:95, 1889.

This observation of Coats attracted no attention and the condition remained unknown till the article of W. H. Schultze[2] in 1912. Schultze described a case of diabetic lipemia in which the splenic pulp was almost completely replaced by large cells with foamy cytoplasm. In fresh, unstained sections these cells appeared filled with shiny droplets, while in alcohol preparations they appeared vacuolated, owing to the presence in the cell body of a lipoid substance. This lipoid was isotropic, not colored by sudan or osmic acid but intensely stained by the Smith-Dietrich method and by Weigert's medullary sheath stain. He therefore considered the substance, following Kawamura's classification, to be "a lipoid in the narrower sense," i. e., not containing any considerable amount of either glyceryl or cholesterol esters. Schultze believed the large cells to be derived from the reticular elements and not from the sinus endothelium, which was intact though compressed. The condition was entirely confined to the spleen, no other organs containing the large cells. Following the article of Schultze, instances of lipoid cell infiltration of the spleen in diabetes were published by Lutz[3] (two cases), Marchand,[4] Williams and Dresbach,[5] Eppinger[6] and Fahr and Stamm,[7] some of which present significant deviations from the findings of Schultze.[8] The condition appears to have been very rare, and probably will become even rarer with the introduction of insulin, under the influence of which diabetic lipemia rapidly disappears. In this paper we desire to consider the interpretation of the lesion in the spleen and its relation to certain other morphologic changes likewise attributable to disturbances in lipoid metabolism. Our attention was drawn to the condition by the following case, studied in the Montefiore Hospital:

REPORT OF CASE

Millie G., aged 6, was admitted to the medical division suffering from diabetes mellitus. Her diabetes was of the extreme severity seen in early childhood. As it was before the days of insulin, it was impossible to control completely her sugar excretion, which ran as high as 177 gm. per day though she weighed only 38 pounds (17.2 kg.). Ketonuria also was usually present; as much as 3.8 gm. of acetone was excreted daily. It was noted that "the color

2. Schultze: Ueber grosszellige Hyperplasie der Milz bei Lipoidaemie, Verhandl. d. deutsch. path. Gesellsch. **15**:47, 1912.

3. Lutz: Ueber grosszellige Hyperplasie der Milzpulpa bei diabetischer Lipaemie, Beitr. z. path. Anat. u. z. allg. Path. **58**:273, 1914.

4. Marchand: München. med. Wchnschr. **62**:19, 1915.

5. Williams, J. R., and Dresbach, M.: A Fatal Case of Diabetes Mellitus Associated with Large Cell Hyperplasia, Am. J. M. Sc. **153**:65 (Jan.) 1917.

6. Eppinger: Die Hepato-lienalen Erkrankungen, Berlin, 1920, p. 513.

7. Fahr, T., and Stamm, C.: Zur Frage der sogenannten Lipoidzellen-hyperplasie, Klin. Wchnschr. **3**:1206 (July 1) 1924.

8. After the completion of this paper a new clear-cut case, the second in the American literature, was reported by Smith, Margaret G.: Hyperplasia of Lipoid Holding Cells in Diabetes with Lipemia, Bull. Johns Hopkins Hosp. **36**:203, 1925. Her findings are in close accord with those of Schultze.

of the skin was that of a low grade jaundice." The edge of the liver was palpable on deep inspiration, but the spleen was not felt. After a stay of seventeen months in the hospital, the child died of diabetic coma, Oct. 21, 1920.

The necropsy[9] was performed by Dr. David Secof. The significant findings were briefly as follows:

On the palms, backs of the elbows, soles of the feet and, to a less extent, on the reverse surfaces of these parts was a discrete and grouped papular eruption, the individual papules varying in size from 1 to 3 mm. The older lesions were a bright yellow, the color characteristic of the eruption xanthomatosis diabeticorum.

When the heart was opened, the existence of lipemia was noted; a greasy, yellowish white layer of fat separated from the blood.

In the endocardium there were numerous slightly elevated, bright yellow patches, each one several millimeters in diameter. On the aortic cusp of the mitral valve was a soft, bright yellow plaque involving the greater portion

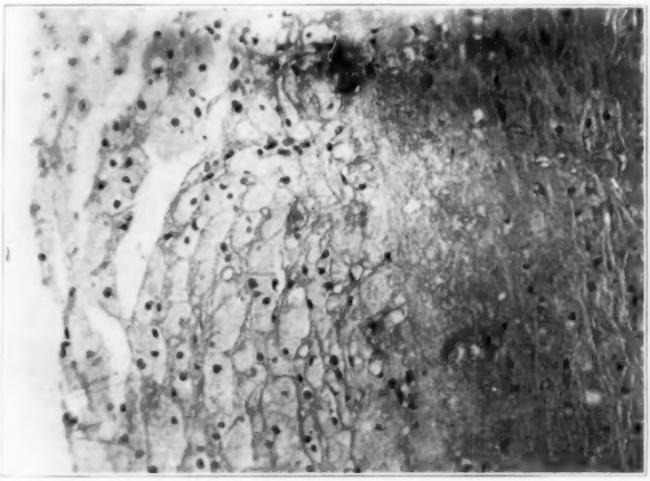

Fig. 1.—Section of aorta stained with hematoxylin and eosin; high dry power, showing the large lipoid cells in the intima.

of this leaflet. In the intima of the arch of the aorta, and more prominently in its abdominal portion, were scattered very bright yellow, soft, opaque nodules. Microscopically, these nodules were seen to be made up of closely packed polyhedral or round cells (Fig. 1). Most of these were very large, but there were small ones and various intermediary sizes. Each of these cells had a single small nucleus, often eccentric or pressed to the periphery, imparting a signet ring appearance to the cell. The cell body appeared transparent in the paraffin sections, and under the high power was seen to have a "foamy" structure. In unstained sections the cytoplasm was seen to be filled with shiny droplets; these stained intensely reddish yellow with sudan. By the method of Smith and Dietrich, many of the cells stained steel blue but not very

9. After being for some months in formaldehyd, the rather large tissue blocks were unfortunately put in alcohol. This apparently did not interfere with the lipoid reaction for the lipemic blood in all the sections stained intensively with sudan.

deeply. The polarization microscope showed that many of these cells contained an anistropic body. It was seen that some, at least, of the large cells were derived from the endothelial cells, for by following the endothelium between the nodules, various stages between the normal flat cell and the large elements filled with lipoid were to be made out. A few mononuclear wandering cells also were present in the intima; whether these cells were likewise concerned in the genesis of the large lipoid cells is difficult to say. In a few areas, the outline of the large cells was indistinct and the nuclei could not be seen, their lipoid content coalescing to form larger accumulations. The elastic tissue

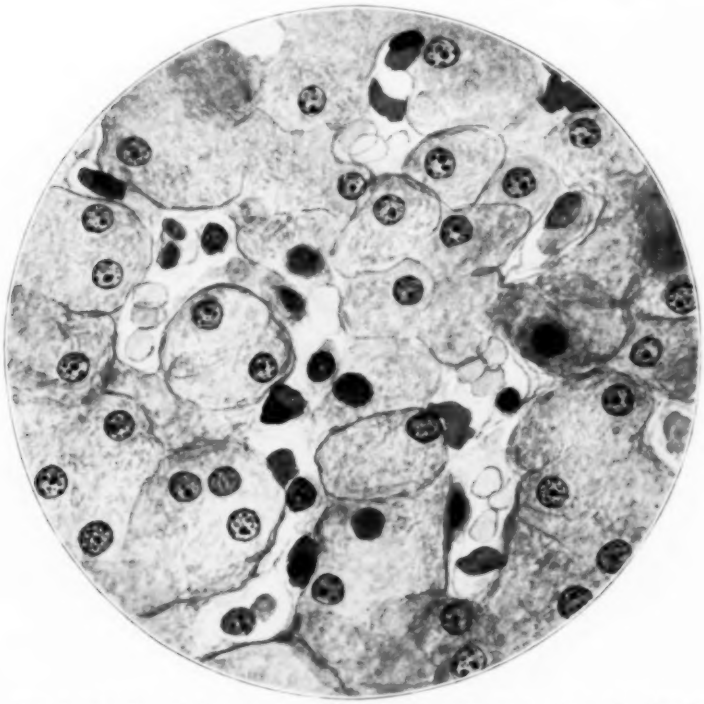

Fig. 2.—Section of liver stained with hematoxylin and sudan, showing the Kupffer cells loaded with lipoid; oil immersion.

of the media was unchanged. The blood in the vasa vasorum of the adventitia and outer media stained intensely with sudan and by the method of Smith and Dietrich.

The liver weighed 850 gm. and was fatty on section. Microscopically (Fig. 2) the liver cells were seen to contain a small amount of finely divided fat. The Kupffer cells were very much enlarged. In the paraffin sections the cell body stained but faintly, appearing pale, but not presenting the "foamy" appearance of the large cells in the spleen. On the other hand, in frozen sections stained with sudan it was colored orange red, and blue black in the Smith-Dietrich preparations. Some of the cells contained an anisotropic body. The blood in the capillaries took the sudan and Smith-Dietrich stains very markedly, so that in the latter preparations the capillaries appeared as though filled with a black injection mass (Fig. 3).

The capsule of the spleen was thin, and it was of average consistency. A section of the spleen presented a firm, dull grayish surface. The trabeculae were perhaps slightly more prominent than the average. The malpighian bodies were not conspicuous. Most striking was the great increase in gray pulp. Near the spleen there was a filbert sized accessory spleen, similar in appearance on section.

In the paraffin sections, it was seen that the malpighian bodies were very small and widely separated. The pulp was almost completely replaced by large, transparent cells, round or polyhedral in shape (Fig. 4). The nucleus was small, stained deeply and was often eccentric. A few of the cells had two nuclei, never more. Under the high power it was seen that the cell body had a foamy appearance, due to the presence of minute circular spaces bounded by a pink staining wall. In some of the cells, these minute spaces had coalesced so as to form large circular vacuoles, which occasionally

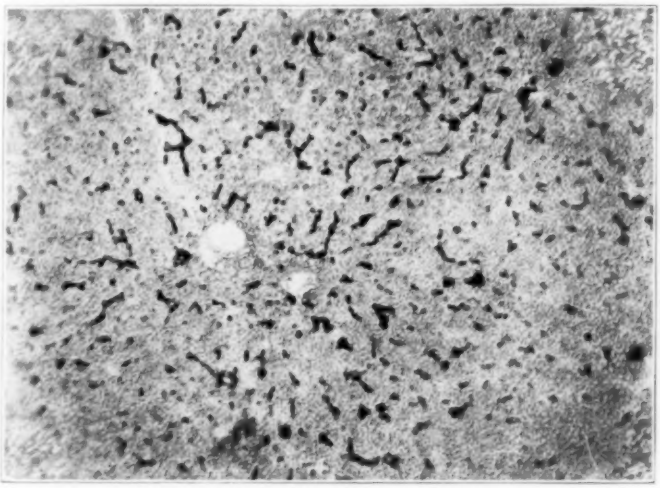

Fig. 3.—Section of liver stained by method of Smith and Dietrich. The lipoid in the capillaries is stained intensely black.

occupied almost the entire cell body. The vacuoles were empty in the paraffin preparations, their contents having been dissolved out in the preparation of the section. In unstained preparations the cells appeared filled with shiny, dark granules. In the sudan sections the blood in the vessels was stained orange red, and around the vessels collections of rather small cells which also stained with sudan were often to be seen. The large cells that had replaced the pulp did not stain with sudan. In the Smith-Dietrich preparations a similar result was obtained; the only positive staining obtained was that of the blood in the vessels and a small number of cells around the vessels. The large cells did not give a lipoid reaction at all, or merely very faintly. Only a few sinuses could be made out, and these were compressed. Their lining endothelium seemed intact. The large cells were apparently derived from the reticulum cells; whether or not the sinus endothelium also gave rise to these cells could not be said from our sections. There was considerable hyalin-fatty change of the intima of the smaller arterioles, giving a positive sudan stain.

The lymph glands were not enlarged. No lipoid cells were seen in the mesenteric and bronchial glands that were removed.

The cells of the cortex of the suprarenals contained rather less lipoid than usual, and that mostly in the glomerular layer.

The pancreas was of average size, the consistency less than usual. The head and a portion of the body appeared digested. There was an area of old hemorrhage in the center. Several sections showed fairly well preserved tissue but a striking absence of islands. No lipoid cells were seen.

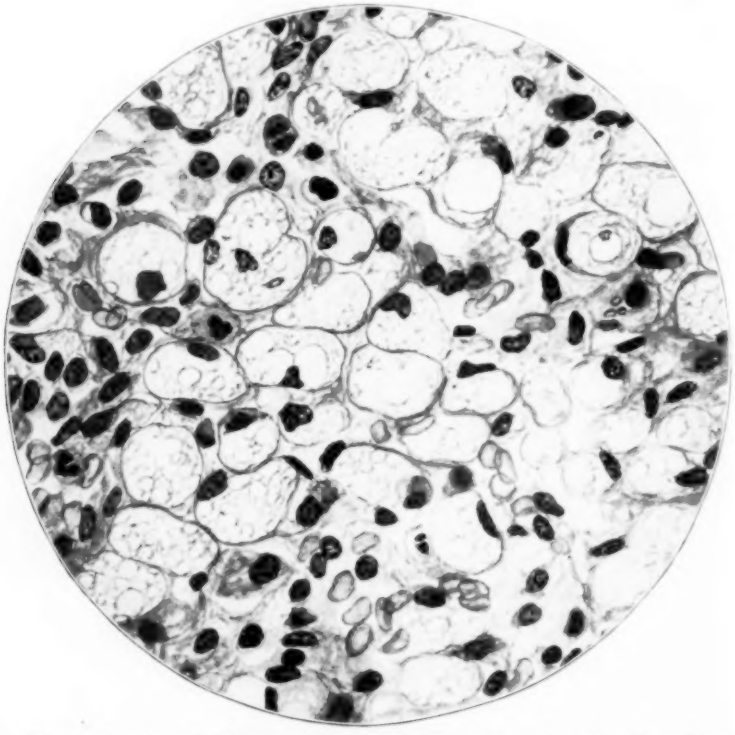

Fig. 4.—Section of spleen stained with hematoxylin and eosin. The almost complete replacement of the splenic pulp by the large lipoid cells (foam cells) is shown; oil immersion.

The glomerular and intertubular capillaries of the kidneys contained large amounts of sudan staining fat. The epithelium of the proximal convoluted tubules contained numerous fine droplets, mostly at the base of the cell, which stained red with sudan. The epithelial cells of the loops of Henle appeared strikingly transparent with well demarcated borders, owing to the presence of large amounts of glycogen in the cytoplasm.

The other organs showed no relevant changes, aside from the large amount of fat in the blood contained in the vessels. Large lipoid cells were not noted in any of the other organs. The bone marrow and central nervous system, unfortunately, were not obtained.

The significant features of the foregoing case may be summarized briefly as follows: A child of 6 years with severe diabetes developed acidosis and died in coma. At the necropsy it was seen that a marked lipemia existed. Aside from the changes in the pancreas to which the diabetes was due, there were found the following lesions which we desire to consider in their relations to the lipemia and to one another.

1. Extensive infiltration of the splenic pulp by large cells containing lipoid.

2. Hypertrophy of the Kupffer cells, which contain much lipoid.

3. Yellow patches in the intima of the aorta and the endocardium, composed of lipoid cells.

4. Xanthomas of the skin.

5. A yellowish discoloration of the skin, the so-called xanthosis.

THE LIPOID CELLS IN THE SPLEEN

That the spleen is concerned in lipoid metabolism is not immediately obvious, for in the normal spleen neither neutral fat nor lipoid can be demonstrated by histochemical reactions. But several observers (Soper,[10] Eppinger and King,[11] and Siegmund[12]) have noted that following splenectomy in dogs and rabbits there is a rise in the neutral fat, cholesterol and phosphatid content of the blood. In man the results reported are discordant, some authors describing a similar rise in the blood lipoids following splenectomy, while others have not observed this.[13] It would seem that splenectomy is not suited to give us information as to the part played by the reticulo-endothelial cells of the pulp in lipoid metabolism, for these form only a portion of the entire reticulo-endothelial apparatus, and the other parts apparently quickly compensate for them in lipoid metabolism much as they do in the breaking down of hemoglobin.

Of much greater significance are the results obtained by lipoid feeding. In his well known experiments, Anitschkow[14] fed rabbits cholesterol dissolved in sunflower oil over long periods of time. In these animals, in addition to similar changes in the aorta, bone marrow and liver, he

10. Soper: Beziehungen der Milz zum Cholesterinstoffwechsel, Beitr. z. path. Anat. u. z. allg. Path. **60**:232, 1915.

11. King, J. H.: Studies in the Pathology of the Spleen, Arch. Int. Med. **14**:145 (Aug.) 1914.

12. Siegmund: Milzapparat und Blutlipoide, München. med. Wchnschr. **68**: 1035, 1921.

13. Dubin, H., and Pearce, R. M.: A Note on the Blood Fat Before and After Splenectomy, Arch. Int. Med. **18**:426 (Sept.) 1916.

14. Anitschkow: Ueber experimentell erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Beitr. z. path. Anat. u. z. allg. Path. **57**:201, 1914.

found that the splenic pulp was almost completely replaced by large "foam cells," loaded with sudan staining, anisotropic lipoid, mainly cholesterol esters. Comparison of Anitschkow's drawings with our preparations leaves no doubt of the morphologic similarity of the cells in the spleen of his rabbits with those found in human diabetic lipemia. Anitschkow himself considered the cells in the spleen of Schultze's case as identical with those which he had produced experimentally in the rabbit.

We have mentioned above that in Anitschkow's experiments the lipoid contained in the large cells of the spleen is identical with that fed the animal and present in excess in the blood. In this respect, the human condition seems to differ somewhat from the experimental. It is known that in diabetic lipemia the neutral fat, cholesterol and phosphatid fractions of the blood lipoids all increase, the greatest rise being in the neutral fat. In accord with this universal increase in the different blood lipoids, in our case the blood in the lumen of the splenic vessels stained orange red with sudan, steel blue by the Smith-Dietrich method and exhibited double refraction through crossed Nicols. Similar reactions were given by some rather small fat phagocytes in the immediate vicinity of the vessels, but the great majority of the large cells did not stain with sudan, only faintly or not at all in the Smith-Dietrich preparations, and contained no anisotropic body.

In Schultze's case of diabetic lipemia, the large cells likewise did not stain with sudan or exhibit double refraction, but did stain intensively by the Smith-Dietrich method. Identical reactions were obtained in one of Lutz's cases, but in his other case and that of Williams and Dresbach many (though not all) of the large cells contained sudan staining and anisotropic lipoid bodies. It is far from clear why in our case the lipoid which stained so well while still in the blood no longer gave the same staining reactions after being stored in the large cells of the spleen. One may advance such purely hypothetic explanations as chemical combination with proteins, changes in the physical state of solution, or elaboration into more complex lipoid bodies, but there seems to be no convincing evidence for any of them. In this connection it is important to bear in mind that the so-called lipoid staining reactions are often poor indicators of which particular lipoid substance is present.

THE KUPFFER CELLS

Normally, the Kupffer cells do not contain histologically demonstrable lipoid. Roessle[15] has pointed out that it is very common to find the Kupffer cells containing lipoid in diabetes; it is not unusual to find

15. Roessle: Ueber die Leber beim Diabetes, Verhandl. d. deutsch. path. Gesellsch. **11**:334, 1907.

anisotropic cholesterol esters in these cells in the same disease. This, however, is not universally true; we have recently seen a patient with diabetes dying in coma in whom, though there was extreme deposition of glycogen in the liver cells, the Kupffer cells contained no lipoid. But in the lipemic case reported above, the Kupffer cells were much enlarged; their cell bodies were filled with lipoid which stained both with sudan and by the method of Smith and Dietrich, and some exhibited double refraction, thus differing essentially from the large cells in the spleen. The liver cells themselves contained but little fat.

CHANGES IN THE AORTA AND ENDOCARDIUM

It was mentioned above that the intimal patches are composed of large cells morphologically like those in the spleen but staining deeply with sudan and containing an anisotropic body. It was also seen that some, at least, of these cells are derived from the endothelium; whether other cells also are concerned in their origin could not be said. Anitschkow [16] was able to produce almost precisely the same changes by feeding rabbits cholesterol dissolved in sunflower oil. The cells shown in his illustrations are similar to those in our sections and their staining reactions are the same. He was unable to determine the precise derivation of these cells. In human pathology the existence of these cells in the aortic intima is well known in atherosclerosis, in which they represent wandering cells that have resorbed lipoid that has been pressed into the interstices of the intima from the blood plasma. Large collections of such "xanthoma" cells have been described in the intima of the central artery of the retina in hemorrhagic glaucoma.[17]. In one of Lutz's cases of diabetic lipemia, the presence of large lipoid cells in the aortic intima is mentioned. The correlation of such "xanthomas" of the aorta with xanthomas of the skin was noted by Pavy [18] as long ago as 1866. A number of cases have been reported [19] in which cardiac murmurs were caused by xanthomas of the valvular endocardium. Benda [20] observed extensive xanthomatosis of the pulmonary veins in a case of nephrosis with marked lipoidemia.

16. Anitschkow: Ueber die Atherosklerose der Aorta beim Kaninchen und ueber deren Entstehungsbedingungen, Beitr. z. path. Anat. u. z. allg. Path. **59**:306, 1914.

17. Velhagen: Ueber den Befund lipoidhaltiger Zellen in der Arteria centralis retinae bei einem Falle von haemorrhagischen Glaukom, Beitr. z. path. Anat. u. z. allg. Path. **57**:38, 1914.

18. Pavy: On a Case of Vitiligoidea Plana et Tuberosa, Guy's Hosp. Rep. **12**:276, 1866.

19. Low: Xanthoma Tuberosum Multiplex with Lesions in the Heart and Tendon Sheaths, Brit. J. Dermat. **22**:109, 1910.

20. Benda, Henke and Lubarsch: Handbuch der spez. path. Anatomie und Histologie, Berlin **2**:826, 1924.

THE XANTHOMAS OF THE SKIN

Xanthomas of the skin are bright yellow, flat or papular lesions composed of large cells with small nuclei and cytoplasm filled with lipoid so that in paraffin sections they have a characteristic clear or foamy appearance. It was shown by Pincus and Pick [21] that xanthoma cells contain cholesterol esters and therefore are doubly refractive. A more recent investigation by Fahr [22] has revealed that there also are instances in which the predominant substance present is neutral fat. Pollitzer and Wile [23] have found that the formation of a xanthomatous lesion starts with a "proliferation of cells in the immediate neighborhood of the papillary and subpapillary blood vessels," which then take up lipoid. The cells observed are evidently the type of phagocytic wandering cells found around blood vessels and termed by Marchand adventitial cells.

There are two main varieties of cutaneous xanthoma:

1. The isolated xanthoma of the eyelid which is so common in old people. The pathogenesis of the lesion is obscure. In particular, there is no manifest lipemia. However, it is of interest to note in this connection that there seems to be a tendency for localized deposition of cholesterol to occur in old age. Thus, besides the xanthomas of the eyelid, atheroma of the large vessels and arcus senilis are exceedingly common findings in healthy old people, the anatomic basis of which consists in the deposition of cholesterol. The arcus senilis has been reproduced experimentally in the rabbit by cholesterol feeding; [24] it has also been noted in youthful subjects with hypercholesterinemia.[25] The reason why the xanthomas occur on the eyelid is unknown; Lubarsch [26] believes that lymph stasis is an important factor in determining the location of xanthomatous lesions and this may play a part in determining the eyelids as the site of predilection.

2. Xanthoma multiplex. These lesions are readily recognized by their bright yellow and their predilection for the extensor surfaces of the elbows and knees. They are almost always secondary to a lipoidemia. The most common conditions in which lipoidemia occurs are diabetes, obstructive jaundice and, much more rarely, nephrosis, and these are the

21. Pincus and Pick: Zur Struktur und Genese der symptomatischen Xanthoma, Deutsch. med. Wchnschr. **34**:1426, 1908.
22. Fahr: Zur Frage des Xanthoms, Centralbl. f. allg. Path. u. path. Anat. **30**:609, 1920.
23. Pollitzer and Wile: Xanthoma Tuberosum Multiplex, J. Cutan. Dis. **30**:235, 1912.
24. Verse: Ueber einige Organveraenderungen bei der experimentellen Lipo-cholesterinaemie, Verhandl. d. deutsch. path. Gesellsch. f. Chir. **19**:163, 1923.
25. Benda, discussion of Verse (Footnote 24, page 167).
26. Lubarsch: Generalisierte Xanthomatose bei Diabetes, Deutsch. med. Wchnschr. **44**:484, 1918.

diseases in which multiple xanthomas are found. Cases of marked lipoidemia of unknown origin ("idiopathic") with multiple xanthomas have been described.[27] A few instances of multiple xanthomas without hypercholesterinemia have been reported;[28] it seems quite possible that in these cases the neutral fat or phosphatid content of the blood may have been increased, and these may have been the substances present in the xanthomas. We have recently been able to follow the disappearance of extensive xanthomatosis in a young diabetic with lipemia as the blood lipoids diminished under insulin treatment, proving beyond cavil the dependence of the xanthomas on the excess of lipoid in the blood.

THE YELLOWNESS OF THE SKIN

Von Noorden was the first to point out that many diabetic patients have a yellowish discoloration of the skin of the palms, soles and around the mouth which he termed xanthosis diabeticorum. The yellowish discoloration may become universal and is rarely very intense. It has been shown by Hess and Myers,[29] Bürger and Reinhart[30] and Salomon[31] that this discoloration is due to carotin and xanthophyll, two fat soluble pigments (lipochromes) which are present in green vegetables, butter, etc. It has been found further that the yellowish pigmentation of the skin is secondary to a similar coloration of the blood plasma that Salomon terms xanthemia. Hess and Myers have shown that this pigmentation can be produced in healthy children by feeding them large amounts of carrots and other vegetables containing lipochromes; Salomon has done this also in adults. A similar pigmentation may occur in infants fed with cod liver oil. Yellowish discoloration of the palms in acute febrile conditions has been termed by the French "la signe palmaire."

An increase in the blood lipochrome, the necessary condition for xanthosis, may or may not accompany an increase in the blood lipoids (neutral fat, cholesterol, phosphatids), the necessary condition for xanthoma multiplex. In the little girl reported above there were both

27. Burns, F. S.: A Contribution to the Study of the Etiology of Xanthoma Multiplex, Arch. Dermat. & Syph. **2**:415 (Oct.) 1920; also, Fordyce in discussion, p. 428. Arning and Lippmann: Essentielle Cholesterinaemie mit Xanthombildung, Ztschr. f. klin. Med. **89**:107, 1920. An instance of this rare "idiopathic" lipoidemia with very extensive xanthomatosis was recently demonstrated at the Mount Sinai Hospital by Dr. A. A. Epstein.

28. Rosenbloom, Jacob: The Cholesterol and Cholesterol-Ester Content of the Blood in Xanthoma Tuberosum Multiplex, Arch. Int. Med. **12**:395 (Oct.) 1913.

29. Hess, A. F., and Myers, V. C.: Carotinemia: A New Clinical Picture, J. A. M. A. **73**:1743 (Dec. 6) 1919.

30. Bürger, M., and Reinhart, A.: Ueber die Genese der Xanthosis Diabetica, Deutsch. med. Wchnschr. **45**:430 (April 17) 1919.

31. Salomon: Ueber Xanthose der Haut, Wien. klin. Wchnschr. **32**:495, 1919.

xanthoma and xanthosis, but in another case of marked diabetic lipemia recently observed the great lipemia was not accompanied by an increase in lipochrome and the skin was unusually white throughout. Evidently the diet did not contain an excess of vegetable containing lipochrome.

From the foregoing considerations, it is seen that each of the first four findings is secondary to a great increase in blood lipoids. The last mentioned finding, the xanthosis, differs from the others, however, in two essential respects: First, it is due to the accumulation in the blood of specific fat-soluble pigments, lipochromes, and second, instead of being stored within a definite system of cells, as we shall immediately see the lipoids in general are, lipochrome seems to enter almost any variety of cell in which it can dissolve in the cell lipoids.

Consideration of the cells involved in the other four lesions—the reticulum cells of the spleen, the Kupffer cells of the liver, the endothelium and possibly wandering cells in the vascular intima, and the adventitial cells of the small cutaneous vessels—reveals that they all belong to the widely distributed system of cells termed by Aschoff and Landau the reticulo-endothelial metabolic apparatus. The close functional interrelationship of these ubiquitous cells is shown by the fact that after injection into the blood stream of certain dyes (pyrrol blue, trypan red, etc.), they are stored in the reticulo-endothelial system. In cholesterol feeding experiments, the cholesterol is stored in the cells of this system. Similarly, Eppinger [32] has found that in normal animals injected iron is stored in the reticulo-endothelial cells. There is much evidence that the formation of bilirubin from hemoglobin occurs within these same cells. Included in the reticulo-endothelial system are three main classes of cells, genetically closely interrelated:

1. The reticulum cells of the hematopoietic (spleen, bone marrow and lymph glands) and certain other organs, notably the suprarenals.

2. Endothelial cells (including the Kupffer cells of the liver capillaries).

3. The great group of phagocytic cells in the connnective tissues, among which are Ranvier's clasmatocytes of the areolar tissue and Marchand's adventitial cells around the blood vessels.

Cells of this system may enter the blood stream, where they are present as monocytic elements (endothelial leukocytes of Mallory).

In our case we have seen that the reticulum cells of the spleen, the Kupffer cells of the liver, the endothelial cells of the aorta and the adventitial cells of the cutaneous vessels have been filled with lipoid. Similar lipoid storage has been described in cases of lipemia in practically all parts of the reticulo-endothelial system. Thus, Marchand

32. Eppinger: Die Hepato-Lienalen Erkrankungen, Berlin, 1920, p. 67.

found involvement of the reticulum cells of the bone marrow; Williams and Dresbach and Fahr and Stamm of those of the lymph glands, and there have been described in cases of lipemia due to different causes "xanthomas" (i. e., lipoid storage) in the most varied portions of the body (pachymeninges, bile ducts, tendon sheaths, periosteum and various viscera), always apparently originating in the reticulo-endothelial cells. In a case of diabetic lipemia, Kawamura [33] demonstrated the presence of cholesterol esters in the monocytic cells of the blood, which we have mentioned above as partially derived from the reticulo-endothelial system.

From the foregoing case and the facts gathered from the literature, it is seen that when a great excess of lipoid accumulates in the blood, which occurs most usually in diabetes and chronic obstructive jaundice, it is stored within the reticulo-endothelial system. This may result in varied anatomic pictures (which have hitherto not been sufficiently correlated with one another), for the portion of the system in which the lipoid is deposited in an individual case varies greatly without our knowing the reason why. Thus, the reticulum cells of the spleen may be the only portion involved; the lymph glands may also participate, or there may be only xanthomas of the skin, etc. The same holds true of other varieties of reticulo-endothelial storage, for instance, of dyes or of iron. That different staining reactions are given by the stored fat and lipoid in various portions of the reticulo-endothelial system was pointed out above.

The histologic appearance of the spleen in cases of lipoid cell hyperplasia is very much like that observed in Gaucher's splenomegaly, in which the splenic pulp is also replaced by large, clear cells, so that it is not surprising that Schultze, in describing the condition, voiced the opinion that Gaucher's disease is also a disturbance of lipoid metabolism. This view has been supported by Wahl and Richardson [34] on the basis of material studied in conjunction with Knox and Schmeisser, but Mandlebaum and Downey [35] have shown clearly that their cases were not Gaucher's disease. However, it has been pointed out by Mandlebaum [36] and by Pick [37] that the substance contained in the large cells

33. Kawamura: Die Cholesterinverfettung, Jena, 1911, p. 88.

34. Wahl, H. R., and Richardson, M. L.: A Study of the Lipin Content of a Case of Gaucher's Disease in an Infant, Arch. Int. Med. **17**:238 (Feb.) 1916.

35. Mandlebaum, F. S., and Downey, H.: The Cases of Gaucher's Disease Reported by Drs. Knox, Wahl and Schmeisser, Bull. Johns Hopkins Hosp. **27**:109 (April) 1916.

36. Mandlebaum, F. S.: Two Cases of Gaucher's Disease in Adults, Am. J. M. Sc. **157**:366 (March) 1919.

37. Pick, Ludwig: Zur pathologischen Anatomie des Morbus Gaucher, Med. Klin. **18**:1408, 1922; Ueber den Morbus Gaucher, seine Klin., pathologische Anatomie und histo-pathologische Umgrenzung, ibid. **20**:1403 (Oct. 12) 1924.

of Gaucher's disease (the so-called Gaucher substance) never gives lipoid reactions, and that the cells differ somewhat both morphologically and in distribution from those found in cases of lipemia. Mandlebaum states that the demonstration of histochemical lipoid reactions in the large cells in any case immediately rules out the diagnosis of Gaucher's disease. In his recent masterly study of Gaucher's splenomegaly, Pick points out that in this disease the endothelial elements of the reticulo-endothelial system are not involved, though we have seen that they are in cases of lipemia. Considering these well established facts, it would seem that the two conditions have nothing more in common than a superficial morphologic similarity of the large, clear cells making up the lesions. Pick himself considers Gaucher's disease as a "congenital, familial, constitutionally caused anomaly of metabolism akin to alkaptonuria or cystinuria."

But in recent investigations Epstein [38] and Lieb [39] have shown that the "Gaucher substance" stored in the large cells characteristic of the disease contains a considerable proportion of kerasin, one of the cerebrosids; these are complex lipoids and are usually found in association with other lipoid bodies. They also found that the Gaucher cells contain large amounts of alcohol-soluble, but ether-insoluble phosphatids. So it would seem that, despite the negative histochemical findings, *Gaucher's disease is an anomaly of lipoid metabolism in which complex lipoids fail of complete disintegration and elimination and are stored in the histiocytic elements of the reticulo-endothelial system.*

Just as there are various metabolic anomalies in which the intermediary metabolism of protein stops at a certain point (e. g., alkaptonuria, in which the organism is unable to break down homogentisic acid), so there are apparently different disturbances of lipoid metabolism. These may be secondary and acquired, as in diabetes, or primary and constitutional, as in Gaucher's disease. Another primary disturbance of lipoid metabolism has recently been described by Pick [37] under the name of "lipoid cell splenohepatomegaly," by which he understands a "congenital, familial, constitutionally caused anomaly of lipoid, especially phosphatid, metabolism." In all four reported cases, this has led to death within the first two years of life, the striking anatomic finding being the presence of large lipoid cells in various organs. In these cases as well as in diabetic lipemia and Gaucher's disease, the large cells constituting the lesions are merely evidence of storage of different lipoids present as a result of a metabolic derangement.

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38. Epstein, E.: Beitrag zur Chemie der Gaucherschen Krankheit, Biochem. Ztschr. **145**:398, 1924.

39. Lieb, Hans: Cerebrosidspeicherung bei Splenomegalie, Typus Gaucher, Ztschr. f. physiol. Chem. **140**:305, 1924.

SUMMARY

1. In experimental lipoid feeding, the lipoids are stored in the reticulo-endothelial cells. This lipoid storage manifests itself by the occurrence in various organs of lesions that are made up of large, clear cells ("foam cells") filled with lipoid.

2. Lesions identical in structure and distribution with those of experimental lipemia are found in diseases in which the lipoid content of the blood is increased, such as diabetes, obstructive jaundice and nephrosis.

3. These lesions are also made up of large foam cells containing lipoid. The foam cells are derived from the reticulo-endothelial cells, and collections of them may occur in various parts of the body (so-called visceral xanthomas). In the past the various lesions thus produced have not been sufficiently correlated with one another. In the skin they appear in the form of multiple xanthomas.

4. A case of diabetic lipemia is described in which the lipoid storage is manifested by:

(*a*) Almost complete replacement of the splenic pulp by large foam cells.

(*b*) Marked deposition of lipoid in the enlarged Kupffer cells.

(*c*) Yellow patches in the intima of the aorta and the endocardium composed of foam cells.

(*d*) Xanthomas of the skin.

5. The yellowish discoloration of the palms and soles (xanthosis) seen in diabetes is not due to lipemia per se but is secondary to an increase in the lipochrome (carotin and xanthophyll) content of the blood. Increase in blood lipochrome and lipemia may or may not be associated.

6. In both manifest lipemia and Gaucher's disease the lesions are composed of cells of the reticulo-endothelial apparatus in which lipoids are stored. But in Gaucher's disease the disturbance of lipoid metabolism is primary and apparently constitutional; it is morphologically manifested by the storage in the histiocytes of cerebrosids and other complex lipoids which do not give the lipoid staining reactions. In the lipemic cases, the derangement of lipoid metabolism is secondary (diabetes, icterus, etc.) and the lipoids found in the reticulo-endothelial cells are those which circulate in excess in the blood (neutral fat, cholesterol and its esters, and phosphatids).

RENAL INJURIES BY AMINO-ACIDS *

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It has been shown by Newburgh and his collaborators [1] (1919, 1923) that high protein diets produce renal injury in rabbits, and by Polvogt, McCollum and Simmonds [2] (1923) that similar diets have a harmful effect on the kidneys of rats. In explanation of this fact, a number of possibilities present themselves for consideration, among which are: (1) poisonous products arising from the action of bacteria on the food in the intestine; (2) the absorption of foreign protein forced into the blood by the excess in the intestine; (3) the excretion of an acid urine from diets high in certain proteins; (4) extra work required of the kidney by the increased nitrogen metabolism, and (5) lack of vitamins. No evidence in favor of any of these explanations was obtained.

In a previous article, it was suggested that the amino-acids themselves might be the source of the renal injury. That both the absorption and the excretion of amino-acids by the kidney is increased by the ingestion of large amounts of protein has been clearly demonstrated by Levene and Van Slyke [3] (1912) and by Folin and Berglund [4] (1922). This article deals with the effects on the kidney of the administration of some of the amino-acids.

METHODS

In this study, the amino-acids entered the body by the intravenous route. In a few of the earlier experiments with rabbits the amino-acids were given in relatively small amounts of fluid. The development of certain general symptoms without evidence of renal injury in some of these animals suggested to us that they were caused by the hypertonicity of the injected solution. We accordingly increased the dilution so that in every case, when it is not otherwise stated, 20 c.c. of the solution contained 1 gm. or less of the amino-acid. Physiologic sodium

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1. Newburgh, L. H.: Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. **24**:359 (Oct.) 1919. Newburgh, L. H., and Clarkson, S.: Renal Injury Produced in Rabbits by Diets Containing Meat, Arch. Int. Med. **32**:850 (Dec.) 1923.

2. Polvogt, L. M.; McCollum, E. V., and Simmonds, N.: Bull. Johns Hopkins Hosp. **34**:168 (May) 1923.

3. Levene, P. A., and Van Slyke, D. D.: J. Biol. Chem. **12**:301, 1912.

4. Folin, O., and Berglund, H.: J. Biol. Chem. **51**:413 (April) 1922.

chlorid solution was used as the vehicle, and precautions were taken that none of the solutions were acid or more than slightly alkaline, except in the case of Rabbit 1 and in certain experiments with glutamic acid, which are discussed in their proper place.

The rabbits used were selected healthy animals that had not been previously employed for any other laboratory purpose. The solution was injected into the ear vein at body temperature without an anesthetic. Because of the prevalence of chronic kidney disease in adult dogs, only puppies recently weaned were used. A very few were obtained from animal dealers, but most of them were undernourished or the subjects of infection and were therefore unsuitable for our purpose. Nearly all the dogs used in these experiments were secured as follows: Pregnant bitches or mothers with recently born litters were obtained from neighboring farmers. Each family was housed in an individual kennel out of doors. A few days after the puppies were weaned they were used one at a time, the others remaining with the mother. During the experimental period, each dog was kept in a clean metabolism cage or a pen reserved for that purpose. Strict isolation from other dogs that constituted a possible source of infection was maintained. These precautions were so successful that the young animals appeared almost without exception to be entirely healthy. Very satisfactory anesthesia was obtained by the subcutaneous injection of morphin sulphate in doses of from one-quarter to three-quarter grain (0.01 to 0.04 gm.), depending on the size of the dog. The vein to be used in the case of dogs was prepared by cutting down on it with the usual surgical precautions. All dogs marked with the same capital letter following the number were litter mates.

In the case of both dogs and rabbits, those showing urinary abnormalities before receiving an amino-acid were permanently rejected and only those whose urine was normal on two successive examinations were used.

The solution was injected slowly with a syringe or allowed to flow in from a buret through a needle, depending on the volume. When the amount of fluid was large, the inflow period was as long as two hours, and when the volume was more than a few cubic centimeters, it was maintained at approximately body temperature. For this purpose the buret was enclosed in a constant temperature jacket.

Following the injection of an amino-acid, the urines were examined daily or oftener for the presence of albumin, casts and red blood cells. We found, as have other workers, that it is not unusual for clear rabbits' urine to become cloudy as the result of boiling and acidulating, and further that the cold acidified specimens would sometimes slowly develop a similar cloud. We therefore concluded that when dealing

with rabbits' urine the ordinary tests for albumin give unreliable evidence of renal disease. While we did not experience this difficulty with dogs' urine, we nevertheless did not consider any urine, either rabbits' or dogs', obtained after the injection of an amino-acid as abnormal which did not show in the centrifugated specimen at least several undoubted casts when examined in the usual way.

We had hoped that careful weighing of the kidneys would give us quantitative information regarding their condition. We found, however, that there was a large variation in the weight of the kidneys of normal animals per kilogram of body weight. We therefore discarded that method of judging the state of the kidneys. Likewise, we found it unsatisfactory to draw conclusions from the gross appearance of the kidneys, since the color variations were great in untreated animals. In a few of the "treated" dogs, the signs of congestion or of cloudy swelling and edema were so striking that there could be no doubt of their presence. Likewise, in the case of several dogs the signs of hemorrhage were so marked that abnormality was certain.

Some of the animals were killed at varying intervals after the administration of the amino-acids and their kidneys immediately placed in fixing solution. The histologic evidence of abnormality was entirely satisfactory.[5] Most of the kidneys so studied were from dogs and the kidneys of untreated litter mates were used as controls.

Some animals whose urine became abnormal after injection were allowed to recover. This gave some information regarding the duration of the injury. Furthermore, recovery from abnormalities that occurred immediately after the injection gave evidence that they were actually due to the injection.

The nonprotein nitrogen of the blood was determined in some of the rabbits. Abnormally high readings yielded further evidence of renal damage following the injection of some of the amino-acids.

EXPERIMENTAL DATA

The experiments with each amino-acid are brought together in one table. Every animal that received an injection is included. Because of intercurrent disease, conclusions could not be drawn from a few of the animals, and these experiments are grouped in a special section of the appropriate table.

Alanin.—When alanin is dissolved in salt solution, a reaction neutral to phenol red results. It is so easily soluble that two of the rabbits received large doses of the alanin in relatively concentrated form

5. The tissues were all fixed in a 4 per cent. solution of formaldehyd. Thin sections were cut from paraffin blocks and were then stained with hematoxylin and eosin.

instead of at the rate of 1 gm. to 20 c.c. of diluent, which we later adopted as our standard in order to obviate certain general disturbances that we attributed to the hypertonicity of the injected solution. In spite of this, none of the animals showed either renal or general disturbances following the intravenous injection of 2 gm. per kilogram.

Leucin.—In order to get leucin into solution, we found it necessary to keep it hot on the water bath for some minutes in a volume of at least 25 c.c. of the salt solution for each gram of the substance and to add 1.15 c.c. standard sodium hydroxid [6] per gram of leucin. The resulting solution was very slightly alkaline in phenol red. None of the three animals that received the leucin gave any evidence of injury, even though Rabbit 30 was given 2.7 gm. per kilogram.

The negative result with the dog is of importance as a control for some of the later experiments with amino-acids that produced renal damage, since the outcome of this experiment demonstrates that the intravenous injection of a large volume of fluid does not injure the kidneys. This dog received 250 c.c. of fluid at the rate of 82 c.c. per kilogram.

Glycin.—This is easily soluble in salt solution and the reaction is neutral. As was the case with alanin, we gave some of the rabbits in this series solutions that were too concentrated. We attributed the sudden death of Rabbit 4 to this cause, and surmised that the prolonged disturbance exhibited by Rabbits 3 and 5 might have a similar origin. At least, none of the animals that were injected with solutions of standard dilution showed any general or renal disturbances. The reasons for not accepting three of the experiments of the series are too evident to require special comment.

We obtained no evidence that glycin, even in doses as large as 3.4 gm. per kilogram, injured the kidney.

Phenylalanin.—The solution of phenylalanin was neutralized with 4 c.c. of standard sodium hydroxid per gram of amino-acid. The slightly abnormal urine obtained from Rabbit 29 following the injection of 1.6 gm. per kilogram was probably not caused by the phenylalanin, since a much larger dose given to Rabbit 41 did not cause the urine to become abnormal. The failure to injure the kidneys of Dog 11 with 3.7 gm. per kilogram left us with no convincing evidence that renal damage is produced by intravenous injection of phenylalanin.

6. The solution of sodium hydroxid used in this and many subsequent experiments was old. It had originally been normal, but was only approximately so when we employed it. We accordingly designate this solution as "standard" rather than "normal." In later experiments, when we speak of "normal sodium hydroxid," we refer to a freshly prepared accurately titrated solution.

TABLE 1.—*Alanin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 15.....	2,200	0.09 (0.2) 5 times in 5 days	Four examinations before injection, negative; six specimens during period of injection, negative	No necropsy	
Rabbit 10.....	?	(5) once in 30 c.c. of solution	Two specimens before injection, negative; four specimens following injection, negative	No necropsy	
Rabbit 16.....	?	(5) once in 25 c.c. of solution	Two specimens before injection, negative; four daily specimens following injection, negative	No necropsy	
Dog 58 K.....	2,800	2 (5.6) once	Two specimens before injection, negative; two specimens following injection, negative	No histologic abnormalities seen in the kidney	Killed 48 hours after injection

* Figure in parenthesis is total single dose.

TABLE 2.—*Leucin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 30.....	1,650	2.7 (4.5) once	Two specimens before injection, negative; three specimens following injection, negative	No necropsy	
Rabbit 32.....	2,250	2.2 (5) once	Two specimens before injection, negative; two specimens following injection, negative	No necropsy	
Dog 59 K.....	3,050	2 (6.1) once	Two specimens before injection, negative; two specimens following injection, negative	No histologic abnormalities seen in the kidney	250 c.c. of solution injected, which was at the rate of 82 c.c. per kilogram

* Figure in parenthesis is total single dose.

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 4 A.....	?	(0.5) once; (1) once in 8 c.c. of solution, interval 24 hours	Two specimens before injection, negative; four specimens following injection, negative	No necropsy	
Rabbit 3.....	1,900	2.2 (4.2) in 17 c.c. of solution once	Urine normal before injection; three daily specimens following injection, negative	No necropsy	Ate little and was lethargic for several days after injection
Rabbit 51.....	2,450	2 (4.9) once	Urine normal before injection; two daily specimens following injection, negative	No abnormalities seen.....	Killed 48 hours after injection
Rabbit 38.....	1,450	3.4 (5) once	Two specimens before injection, negative; two daily specimens following injection, negative	No necropsy	
Dog 2 A.....	7,650	1.3 (10) once	Urine before injection, negative; two specimens following injection, negative	No necropsy	
Dog 53 K.....	2,500	2 (5)	Two specimens before injection, negative; two daily specimens following injection, negative	Slight cloudy swelling; few casts in medulla	Killed 48 hours after injection
			Experiments Not Acceptable		
Rabbit 9.....	2,350	0.17 (0.4) 5 times in five days; two weeks later 2.1 (5) once	Daily examination of urine, negative until two days after large injection, when many casts were seen	No necropsy	Large abscess of neck noted coincident with abnormal urine
Rabbit 4.....	1,600	3.1 (5) in 20 c.c. of solution once	Urine normal before and after injection.....	No necropsy	Convulsion and death 2 hours after injection
Rabbit 5.....	1,650	3 (5) in 20 c.c. of solution once	Three specimens before injection, negative; two specimens following injection showed albumin and casts	No necropsy	Ate little and was lethargic after injection; three days after injection had a convulsion and died

* Figure in parenthesis is total single dose.

TABLE 4.—*Phenylalanin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 29.....	1,800	0.5 (1) once; two days later 1.6 (3) once	Two specimens before injection, negative; on second and third days after second injection, albumin and a few casts were present; thereafter, urine was negative	No necropsy	
Rabbit 33.....	1,500	0.66 (1) twice; interval 48 hours	Two specimens before injection, negative; two specimens following first injection, negative	No necropsy	Sudden death following second injection
Rabbit 41.....	1,750	2.8 (5) once	Two specimens before injection, negative; two specimens following injection, negative	No necropsy	
Dog 11.....	2,700	3.7 (10) once	Two specimens before injection, negative; three specimens following injection, negative	No microscopic abnormalities seen	Killed 3 days after injection

* Figure in parenthesis is total single dose.

Glutamic Acid.—A number of the experiments in this series could not be accepted because the animals either died at the end of the injection or were ill following it. All of these animals received unneutralized solutions of glutamic acid. Furthermore, the solutions were too concentrated. The injection of dilute solutions made neutral to phenol red with standard sodium hydroxid caused no detectable renal injury. We accordingly concluded that the abnormal urine voided by Rabbit 9 was attributable to the acidity of the solution. The data obtained from Dog 57 K are valuable as control material. The large amount of combined alkali, 48 c.c. of standard sodium hydroxid, or more than 14 c.c. per kilogram, used to neutralize the glutamic acid did not damage the kidneys, even though the dog developed manifest tetany toward the end of the experiment.

Arginin.—The alkaline solution formed by dissolving arginin in salt solution was neutralized against phenol red with standard hydrochloric acid solution at the rate of 3.5 c.c. per gram of the amino-acid. The five acceptable rabbit experiments taken together give satisfactory evidence of the injurious effect of arginin on the kidney. But the injury is mild as compared with the effect of some of the amino-acids to be dealt with later, and arginin is apparently incapable of damaging the dog's kidney even when large doses are injected.

Aspartic Acid.—The acid solution was neutralized against phenol red with 8 c.c. of standard sodium hydroxid per gram of the amino-acid. The rabbit injections show that well marked renal injury is produced in them by a single injection of 1 gm. per kilogram. As the result of an injection of that size, Rabbit 56 voided urine containing casts for eight days subsequent to it. The evidence obtained from dogs is insufficient to prove that aspartic acid injures their kidneys in the dosage employed.

Here again we obtained evidence that the presence of a very large amount of alkali added to the injection fluid to neutralize the acidity of an amino-acid does not injure the kidneys. In six days Dog 25 D received 55.2 c.c. of standard sodium hydroxid twice, followed two days later by 83.2 c.c. of standard sodium hydroxid, a total of 193.6 c.c., or 56 c.c. per kilogram, added to a solution of aspartic acid to make it neutral to phenol red. This animal exhibited no urinary abnormalities.

Lysin.[7]—The lysin was injected in the form of the dichlorid, but the dosage is calculated as the lysin itself. We would have liked to perform more experiments with it, but were unable to obtain any more of it.

7. We are indebted to Professor H. B. Lewis for the lysin dichlorid used in these experiments.

TABLE 5.—*Glutamic Acid*

TABLE 5.—*Glutamic Acid*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 11.....	?	(1) once; not neutralized	Two specimens [illegible] and [illegible] injection were negative	No necropsy	
Rabbit 39.....	1,350	3.7 (5) once	Two specimens before injection, negative; two specimens following injection, negative		
Dog 57 K.....	3,300	2 (6.6) once	Two specimens before injection, negative; two daily specimens following injection, negative	No histologic abnormalities seen in the kidney	48 c.c. of normal sodium hydroxid were required to neutralize the glutamic acid; violent tetany occurred at end of injection
			Experiments Not Acceptable		
Rabbit 12.....	?	(2) in 10 c.c. of solution not neutralized	Urine normal before injection; four daily specimens following injection, negative	No necropsy	Ill for several days after injection
Rabbit 14.....	?	(3) in 15 c.c. of solution not neutralized	Two specimens before injection, negative; five specimens following injection, negative	No necropsy	Ill for several days after injection
Rabbit 7.....	?	(5) in 30 c.c. of solution not neutralized	Three specimens before injection, negative; urine voided fifteen minutes after injection showed albumin and casts	No necropsy	Died in convulsions shortly after injection
Rabbit 9.....	?	(5) in 30 c.c. of solution not neutralized	Two specimens before injection, negative; day after injection, urine contained albumin and casts	No necropsy	Ill following injection
Rabbit 15.....	?	(5) in 30 c.c. of solution not neutralized	Two specimens before injection, negative; three specimens following injection, negative	No necropsy	Ill for several days following injection

* Figure in parenthesis is total single dose.

TABLE 6.—*Arginin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 55.....	3,150	0.5 (1.6) once	Two specimens before injection, negative; second day after injection, urine contained much albumin but no casts; thereafter, urine was normal	No necropsy	
Rabbit 58.....	2,650	1 (2.6) once	Urine normal before and after injection.....	No necropsy	
Rabbit 53.....	2,750	1 (2.7) once	Two specimens before injection, negative; two daily specimens after injection showed albumin and many casts	Many old linear scars but no acute changes	Killed 48 hours after injection; liver was moderately affected by coccidiosis; lungs presented a number of granular areas which exuded pus on section
Rabbit 60.....	1,950	1.5 (3) once	Urine was negative before and after injection...	No necropsy	
Rabbit 52.....	3,400	2 (6.8) once	Two specimens before injection, negative; two daily specimens following injection showed much albumin and many granular and hyaline casts	Many old linear scars causing bands of contraction in cortex	Killed 48 hours after injection
Dog 24 C.....	1,800	2 (3.6) twice, interval 48 hours; 2.5 (4.6) once, interval 48 hours	Two specimens before injection, negative; five specimens during injection period, negative	No necropsy	
Dog 62 L.....	2,500	2 (5) once	Urine was negative before and after injection...	No abnormalities	Killed 48 hours after injection
			Experiment Not Acceptable		
Dog 20.....	2,050	2 (4.1) twice, interval 48 hours	Urine was negative before and after injection...	.....	Morning after second injection, dog had a bloody diarrhea; no further observations made

* Figure in parenthesis is total single dose.

TABLE 7.—*Aspartic Acid*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 59	1,850	0.5 (0.92) once	Two specimens before injection, negative; occasional casts on day after injection; thereafter, urine again normal	No necropsy	
Rabbit 56.....	2,700	1 (2.7) once	Two specimens before injection, negative; for the first five days after injection the urine contained albumin and many hyaline, granular and cellular casts; thereafter, casts were present in decreasing numbers until the ninth day when the urine was again normal	No necropsy	
Rabbit 54.....	2,500	2 (5) once	Urine normal before injection; three hours after injection, albumin and many casts present; two specimens on day following injection contained many granular, hyaline and cellular casts	Several deep linear scars extending from capsule to medulla; numerous casts	Killed 24 hours after injection
Dog 45 G.....	5,250	1.8 (9.7) once	Two specimens before injection, negative; one specimen 48 hours after injection, negative	No microscopic abnormalities were seen	Killed 2 days after injection
Dog 17.....	5,400	2 (10.8) once	Two hours after injection, albumin and a few casts noted; 18 hours after injection, both albumin and a few casts were found; thereafter, casts were not seen	No necropsy	
Dog 25 D.....	3,450	2 (6.9) twice, interval 48 hours; 3 (10.4) once, interval 48 hours	Urine normal before and after injections.....	No necropsy	
			Experiments Not Acceptable		
Rabbit 57.....	2,250	0.5 (1.1) once	Two specimens before injection, negative; day after injection, much albumin and many casts were present	.....	Day after injection, purulent nasal discharge; next morning found dead
Rabbit 50.....	2,800	2 (5) once	Day following injection, much albumin and many casts	.....	Found dead morning after injection; necropsy revealed bronchopneumonia
Dog 16.....	4,200	3.0 (12.6) once	Four samples before injection, negative.....	.....	Found dead morning after injection

* Figure in parenthesis is total single dose.

TABLE 8.—*Lysin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 49.....	1,800	0.18 (0.33) once, interval 24 hours; 0.11 (0.2) once	Before injection, negative; after first injection a few casts were seen; 48 hours after second injection, many casts were found; each of seven examinations during next eleven days showed numerous casts; albuminuria was variable	No necropsy	
Rabbit 50..	2,000	0.16 (0.33) once, interval 24 hours; 0.27 (0.54) once, interval 48 hours; 0.2 (0.4) once	Two specimens before injection were negative; 48 hours after second injection, albumin and a few casts present; albuminuria continued three days, but casts were not seen again	No necropsy	
Dog 46 H.....	3,550	0.6 (2.2) once	Two specimens before injection, negative; morning after injection, urine negative; 48 hours after injection, albumin and casts present	No histologic abnormalities were seen	Killed 48 hours after injection
Dog 33.....	2,850	1.35 (3.8) once	Two specimens before injection, negative; urine remained normal after injection	Congestion; edema; vacuolar degeneration of epithelial cells lining straight tubules	Four days after injection was killed
Dog 42 G.....	3,000	1.3 (4.0) once	Two specimens before injection, negative; three specimens during 48 hours following injection each showed numerous granular and cellular casts	Moderate cloudy swelling and granular degeneration of epithelium of convoluted tubules	Killed 48 hours after injection
			Experiment Not Acceptable		
Rabbit 48.....	2,050	0.65 (1.3) once	Negative before injection.....	.....	During injection had a convulsion and died

* Figure in parenthesis is total single dose.

TABLE 9.—*Histidin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 4.....	1,400	0.10 (0.14) every fourth day; ten injections	Three specimens before injection, negative; 48 hours after first injection, a few casts were seen; albumin did not appear until after third injection; both albumin and casts increased slowly until the albuminuria became very heavy and the casts very numerous; both still marked eight days after last injection	Reference should be made to protocol of Rabbits 4 and 5	Killed 8 days after last injection
Rabbit 6.....	2,300	0.06 (0.14) every third day; five injections followed by 0.15 (0.34) every third day; six injections	Four specimens before injection, negative; it remained normal throughout the first series of injections until the last day when a few casts were noted; during the second series of injections, casts were present at every examination	Most of the glomeruli showed delicate adhesions between tufts and capsule; casts were numerous	Three days after last injection, blood nonprotein nitrogen was 33 mg. per 100 c.c. of plasma
Rabbit 7.....	2,300	0.06 (0.14) every third day; five injections followed by 0.15 (0.34) every third day; six injections	Four specimens before injection, negative; remained negative throughout first series of injections; casts appeared after first injection of second series, gradually increased in numbers, and were regularly found for four weeks after last injection; thereafter, urine was again negative	No necropsy	Two days after last injection, blood nonprotein nitrogen was 36 mg. per 100 c.c. of plasma
Rabbit 3.....	1,500	0.23 (0.34) daily; four injections	Urine normal before injection; a few casts were found after second injection; they were found repeatedly on subsequent examinations	No necropsy	Twenty-four hours after last injection, blood nonprotein nitrogen was 66 mg. per 100 c.c.
Rabbit 2.....	1,200	0.43 (0.52) once	Urine before injection showed neither albumin or casts; day after injection, albumin but no casts were found; next day, both albumin and casts were found	A few casts; otherwise not abnormal	Killed 48 hours after injection
Rabbit 1.....	1,450	0.5 (0.69) in 6 c.c. of solution (not neutralized) once	Urine normal before injection; day after injection, urine contained much albumin and many casts; both were abundantly present for next seven days, when urine again became normal	No necropsy	Ate nothing for 48 hours following injection; had loose movements for three days after injection
Dog 55 K.....	3,100	0.33 (1.0) every other day; five injections	Two specimens before injection, negative; during injection period a few casts were found in three specimens and were absent in three	The convoluted tubules stand out because of the deeper pink stain of their lining cells, which are swollen and hazy and in places frayed out and granular; a few nuclei are pycnotic	Killed 48 hours after last injection
Dog 4 A.....	7,050	0.5 (3.4) twice, four day interval	Urine normal before injection; heavy albuminuria and many casts were present day after first injection and continued for eight days after second injection, when urine again became normal	No necropsy	
Dog 49 I.....	3,650	1.38 (5) once	Two specimens before injection, negative; day after injection, urine contained numerous granular and epithelial casts	The cortical tubules showed moderate cloudy swelling; scattered casts seen	Killed 48 hours after injection
Dog 61 K.....	2,900	1.24 (3.6) once	Two specimens before injection, negative; first day after injection, urine contained a very few casts and no albumin; the second day casts were more numerous and albumin was present; the third day there were many casts and albumin	No histologic abnormalities seen in kidneys	Killed third day after injection

* Figure in parenthesis is total single dose.

When lysin dichlorid is dissolved in salt solution, an acid reaction is produced. We used 1.9 c.c. of standard sodium hydroxid per gram of the amino-acid to make the reaction of the solution neutral to phenol red.

The five successive experiments demonstrate by means of urinalysis, as well as by the microscopic examination of the kidney, that lysin is definitely nephrotoxic. We were unable, with the limited supply of lysin, to determine how small a dose will injure the kidney.

Histidin.—This was used in the form of the dichlorid, but the dosage was calculated as histidin itself. When the dichlorid was dissolved in salt solution, the resulting acidity required 8 c.c. of our standard solution per gram of the amino-acid to obtain neutrality with phenol red or bromcresol purple. The first experiment with histidin was performed on Rabbit 1. This is the only experiment in which the injection fluid was not neutralized. But the striking evidence of kidney injury in this experiment is not attributable to the acidity of the solution (the equivalent of 8 c.c. of standard alkali) since much larger amounts of acid in the form of glutamic acid were injected without evidence of renal injury. Rabbit 15 received the equivalent of 36 c.c.; Rabbit 14, the equivalent of 22 c.c.; Rabbit 12, the equivalent of 14.5 c.c. standard acid as glutamic acid without the occurrence of abnormal urines.

The most interesting data in this series were obtained from the comparative study of Rabbit 4, which received the injections of histidin, and Rabbit 5, which was the control. The accompanying proctocol shows that the repeated intravenous injection of as little as 100 mg. per kilogram of histidin caused serious renal injury.

PROTOCOL

EXPERIMENT 1.—Rabbits 4 and 5, partly grown rabbits, were placed in adjoining metabolism cages in the laboratory, April 25, 1921. Rabbit 4, which weighed 1,400 gm. received repeated injections of histidin dichlorid. Rabbit 5, which weighed 1,700 gm., served as a control. Except for the injections, both rabbits lived under the same conditions. The urine of both rabbits was regularly examined on the same days. After three normal specimens had been obtained from each, Rabbit 4 began receiving the histidin, April 27. From that date until June 6, a total of forty days, he was given ten injections. The histidin dichlorid was dissolved in 5 c.c. of physiologic sodium chlorid solution and neutralized with sodium hydroxid against bromcresol purple as an indicator. The single dose calculated as histidin was 98 mg. per kilogram. The day after the first injection, the urine of Rabbit 4 was still normal. A few casts were seen after the second injection. Albuminuria did not become constant until after the fourth injection, from which time it slowly increased until the tests gave a heavy flocculent precipitate. Casts were always present after their first appearance and gradually increased in numbers until by May 20 they were recorded as very numerous. From June 6, when the last injection was given, until June 15 four specimens from Rabbit 4 continued to show much albumin and many casts. Throughout this whole period, thirty-one examinations of the urine of Rabbit 5 had invariably been negative. June 15, both rabbits were killed by

a blow on the head. Rabbit 4 weighed 1,490 gm. and his kidneys weighed 11.8 gm., or 7.9 gm. per kilogram. Rabbit 5 weighed 1,685 gm. and his kidneys weighed 10 gm., or 5.9 gm. per kilogram. The kidneys of the treated animal, therefore, weighed 2 gm. per kilogram more than those of the control.

The histologic examination of a section of the kidney from Rabbit 4 showed multiple, delicate adhesions between the tufts and Bowman's capsule in the majority of the glomeruli; but there was no exudate in Bowman's space nor was the capsule thickened. In the medulla casts were seen in many places. The microscopic examination of the kidney of Rabbit 5 revealed no abnormalities.

On the other hand, repeated injections of 60 mg. per kilogram (Rabbits 6 and 7) were not productive of abnormal urine.

Examination of the data obtained from the dogs shows that the kidneys of this carnivorous animal were slightly injured by repeated injections of 330 mg. per kilogram (Dog 55 H); that two injections of 500 mg. per kilogram caused greater injury (Dog 4 A), and that single injections of less than 1.5 gm. per kilogram (Dogs 49 I and 61 K) caused abundant evidence of renal injury.

Tyrosin.—In order to get tyrosin into solution in the desired volume we used 10 c.c. of standard sodium hydroxid for each gram of the amino-acid. Such solutions were alkaline to phenol red. The question is therefore pertinent whether the alkalinity is of such a degree that it would in itself be capable of injuring the kidney, regardless of any effect of the tyrosin. The alkalinity of a sample of the solution was measured with the potentiometer by L. A. Philipp of the department of physical chemistry, who found the p_H to be 10.61. Expressed in terms of normal alkali, the tyrosin solution has an alkalinity equal to two thousand five hundredth normal sodium hydroxid. This very slight alkalinity would, on *a priori* grounds, not be expected to harm the kidney. However, we have obtained experimental evidence that large amounts of sodium hydroxid of which the alkalinity has not been reduced in any way, such as is the case in the tyrosin solutions, gives no demonstrable evidence of renal injury.

In a later section dealing with cystin, it will be noted that Dog 28 E received 33.6 c.c. of normal sodium hydroxid in the form of the free alkali. This 8.4 c.c. per kilogram of normal alkali produced no evidence of injury. This injection caused the dog to receive 1.34 gm. of uncombined sodium hydroxid. A like amount of tyrosin solution contains only 0.00054 gm. of uncombined sodium hydroxid.

The following experiment also demonstrates that large amounts of alkali may be injected into the vein of a dog without injuring the kidneys.

EXPERIMENT 2.—Dog 3 A, weighing 7,200 gm., Feb. 20, 1923, at 1:30 p. m. was given morphin sulphate, one-quarter grain (0.01 gm.), and at 2 p. m., 34 c.c. of standard sodium hydroxid plus 0.8 gm. of sodium chlorid made up to 100 c.c. with distilled water was slowly injected into a vein.

February 21, the afternoon urine was slightly acid; there was no albumin, and casts were absent. February 23, 34 c.c. of standard sodium hydroxid prepared as on the previous occasion was injected into a vein. February 25, the afternoon urine showed no albumin and no casts. The first injection site presented a large area of necrosis. February 26, the urine showed no albumin and no casts.

Examination of Table 10 shows that definite evidence of renal injury is obtained following several injections of about 0.2 gm. per kilogram of tyrosin into rabbits.

Larger single injections were followed by the prolonged presence of albumin and casts in the urine. The high values for blood nonprotein nitrogen obtained from Rabbits 20, 17 and 27 afford important evidence of renal injury. The reading of 66 mg. obtained from Rabbit 27 nine days after the injection of 1.8 gm. of tyrosin per kilogram is especially significant.

The dog experiments do not permit any conclusions regarding the smallest dose of tyrosin that will cause renal injury in them. Four of the seven dogs received 2 gm. per kilogram of tyrosin, and in every instance that dose was productive of bloody urine. This fact is of special interest since tyrosin is the only one of the twelve amino-acids thus far studied which has caused red blood cells to appear in the urine.

The microscopic examination of the kidneys from the five dogs that were examined at necropsy, disclosed another feature of great interest. In three (Dogs 15, 23 C and 5 B) of these five dogs, the glomeruli contained important evidence of injury in the form of proliferation of the epithelial cells of Bowman's capsule. No other amino-acid gave us unequivocal evidence of glomerular damage. In the case of Dog 13, it was impossible to decide whether capsular proliferation due to tyrosin had occurred because so many glomeruli had been scarred by chronic kidney disease. The absence of signs of glomerular injury in Dog 22 C may be due to the short interval (twenty hours) between the injection and necropsy, or because this dog received only one injection, whereas the three dogs that showed the glomerular lesions had each received repeated injections over a number of days. Dog 15, whose protocol appears below, is instructive in this respect, since he was dead within twenty hours after the dose of 2 gm. per kilogram, as was Dog 22 C twenty hours after its injection of 2 gm. per kilogram. But Dog 15 had received four small doses of tyrosin preceding the 2 gm. dose and showed the glomerular lesions, whereas Dog 22 C received only the one large injection and lacked the capsular proliferation.

EXPERIMENT 3.—Nov. 8, 9 and 12, 1923, the urine of Dog 15, a puppy that weighed 5,600 gm., contained no casts or albumin. November 12, morphin sulphate, three-quarters grain (0.04 gm.) was injected subcutaneously. One hour later, the animal was tied to a board and a vein in the hind leg was

TABLE 10.—*Tyrosin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 14.....	2,600	0.08 (0.2) daily; six injections; after interval of eight days, 0.19 (0.5) daily; two injections	No casts were seen at any time.....	No necropsy	Killed by second injection of second series
Rabbit 16.....	?	(0.5) daily; two injections	Two specimens before injection, negative; urine, 18 hours after injection, negative	No necropsy	Killed by second injection
Rabbit 21.....	2,300	0.23 (0.5) every third day; five injections	Two specimens before injection, negative; constant albuminuria after first injection; casts first seen after fourth injection	No necropsy	
Rabbit 20.....	?	(0.5) every other day; four injections	Urine remained normal until after third injection, when albuminuria became constant; casts were seen after fourth injection	No necropsy	Blood nonprotein nitrogen was 120 mg. 24 hours after last injection
Rabbit 22.....	2,700	0.18 (0.5) every other day; three injections; after interval of ten days 0.36 (1) once	Two specimens before injection, negative; constant albuminuria after first injection; a few casts were seen after first injection, but not thereafter	No necropsy	
Rabbit 17.....	1,500	0.66 (1) every other day; three injections	Urine normal before injection; constant albuminuria after first injection; casts seen at every examination after third injection	No necropsy	Blood nonprotein nitrogen was 160 mg. 48 hours after last injection; lethargic at this time; died in coma one hour later
Rabbit 18.....	1,800	1.1 (2) once	Marked albuminuria 18 hours after injection; casts first seen three days after injection, they were present in every specimen for next eight days; thereafter, urine was normal	No necropsy	
Rabbit 27.....	2,300	1.8 (4.1) once	Four specimens before injection, negative; six hours after injection, albumin and a few casts were present; for the next nine days there was a heavy albuminuria, and many casts were seen in every specimen	Kidneys not preserved.....	Blood nonprotein nitrogen 9 days after injection was 66 mg. per 100 c.c. of plasma

Dog 2 A.....	6,900	1.4 (10) once	Four specimens before injection, negative; two days after injection, urine contained much albumin and many casts; these abnormalities continued to be present for another 48 hours; thereafter, urine was normal	No necropsy	
Dog 22 C.....	2,450	2 (4.9) once	Two specimens before injection, negative; urine voided during 20 hours following injection was smoky owing to the presence of red blood cells; no casts seen	The lining cells of the convoluted tubules showed granular degeneration and swelling of nuclei; no coagulation in Bowman's space	Killed 20 hours after injection; blood nonprotein nitrogen 33 mg. per 100 c.c. of plasma
Dog 1 A.....	3,300	0.9 (3) once; three days later, 1.5 (5) once	Urine showed albumin but no casts after first injection; 18 hours after second injection, much albumin and many casts were present; both were still found for another 48 hours; thereafter, urine was again normal	No necropsy	
Dog 15.....	5,600	0.5 (2.8) every other day; four injections; after interval of three days, 2 (11.2) once	Urine remained normal throughout the first series of injections; urine voided during the 20 hours following injection of 2 gm. per kilogram was pink, contained many red blood cells but no casts	Protocol of Dog 15 and Figure 1	Found dead 20 hours after last injection
Dog 23 C.....	1,850	0.5 (0.92) every other day; four injections; after interval of three days, 2 (3.7) once; after interval of three days, two injections 48 hours apart of 0.5 (0.92)	Urine remained normal during first series of injections of 0.5 gm. per kilogram; six hours after the injection of 2 gm. per kilogram, pink urine, containing many red blood cells, was voided; during next 48 hours, many casts and red blood cells were present; urine obtained from bladder at necropsy contained many casts	Same changes as those described in detail in protocol of Dog 15 and illustrated in Figure 1	Died about 15 hours after last injection
Dog 5 B.....	2,450	1 (2.5) every third day; three injections after interval of 48 hours, one injection of 0.7 (1.7); 24 hours later, 2 (5) once	Casts first appeared after second injection of 1 gm. per kilogram and continued to death	Same changes as those described in detail in protocol of Dog 15 and illustrated in Figure 1	Animal died at end of last injection
			Experiment Not Acceptable		
Dog 13.....	5,200	2 (10.1) once; after interval of three days, two injections 48 hours apart of 1 (5.2)	Two specimens before injection, negative; day after first injection, smoky urine containing many casts and red blood cells was obtained; urine continued to show many casts to death, 48 hours after last injection	Characteristic microscopic appearance of contracted kidney; this was the only adult dog used	Refused food for 48 hours after first injection; killed 48 hours after last injection; blood nonprotein nitrogen was 52 mg. per 100 c.c. of plasma

* Figure in parenthesis is total single dose.

exposed with the usual surgical precautions. Tyrosin, 2.8 gm., was dissolved in 31 c.c. of standard sodium hydroxid on the water bath. The solution was then brought up to 80 c.c. by addition of 0.8 per cent. salt solution. This solution was then allowed to flow slowly into the vein from a container enclosed in a jacket through which water at about 38 degrees C. circulated. The injection ended at 11:15 a. m. At 4:00 p. m. the dog voided urine containing neither albumin nor casts.

November 13, the urine contained no albumin or casts.

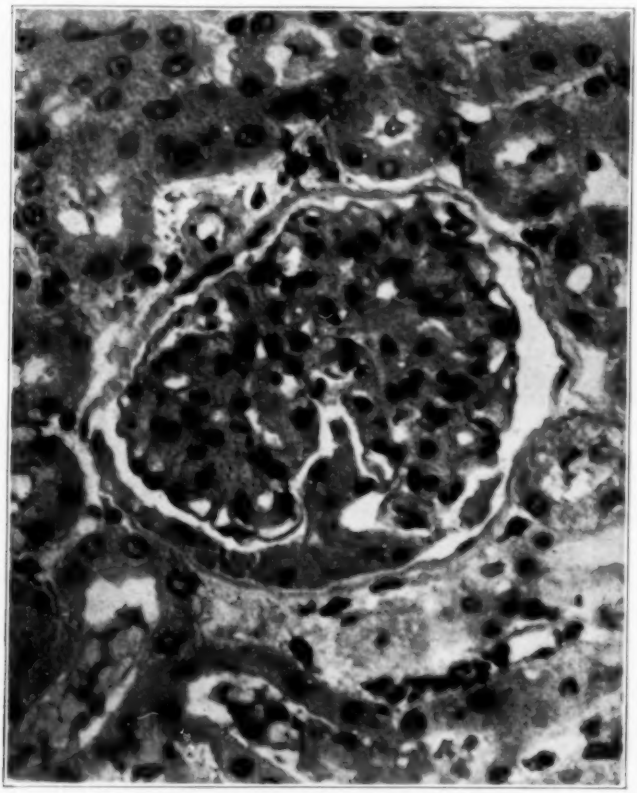

Fig. 1.—Cellular exudate in Bowman's space produced by intravenous injection of tyrosin into a dog.

November 14, at 10 a. m., 2.8 gm. of tyrosin prepared as before was slowly injected into a vein one-half hour after the subcutaneous injection of morphin sulphate, three-fourths grain (0.04 gm.). At 2:30 p. m. the urine contained no albumin but a very few casts.

November 15 and 16, the urine was negative.

November 17, at 10 a. m., 2.8 gm. of tyrosin was injected as before.

November 18 and 19, the urine was negative.

November 19, at 10 a. m., 2.8 gm. of tyrosin was injected as on previous occasions.

November 20, the urine was normal.

November 22, at 11:05 a. m., 11.2 gm. of tyrosin was dissolved in 120 c.c. of standard sodium hydroxid on a water bath and brought up to a volume of 225 c.c. with physiologic sodium chlorid solution. This solution was allowed to flow into a vein in the course of seventy minutes. The injection ended at 11:15 a. m. Toward the end of the injection, irregular twitching of the muscles of the face occurred. At 9 p. m. the dog was quiet, and there was no twitching.

November 23, at 8:30 a. m., the dog was found dead in rigor mortis. The urine collected during the night was pink (laked hemoglobin). There was a heavy albuminuria and the sediment contained many red blood cells but no casts.

Necropsy.—The lungs showed hypostatic congestion. The organs other than the kidneys presented no gross abnormalities. The kidney weighed 43.5 gm. They were purple. On section the surface was bathed in a serosanguinous fluid. The urine obtained from the bladder was pink and contained much albumin, many red blood cells, some crystals of tyrosin, but no casts.

Microscopic examination of a section of the kidney fixed in formaldehyd and stained with hematoxylin and eosin showed that the epithelium of the tubules in the cortex was stained irregularly. The epithelial lining of the convoluted tubules, in particular, was swollen and granular, and the cell margins were no longer distinguishable. Occasional short sections of tubules were seen in which the nuclei had disappeared and the cytoplasm had been changed into a mass of pink staining droplets occupying the lumen. Many of the nuclei of the tubular epithelium were very small, structureless and intensely stained. Nuclear fragmentations were common. A few nuclei were swollen and pale. Casts and desquamated epitheliums were plentiful. Bowman's space in about half the glomeruli contained larger and smaller crescentic shaped and irregular collections of large plump epithelial cells whose nuclei were in varying states of preservation. Some were quite pycnotic, others large and vascular. The cytoplasm was granular and deeply stained. It closely resembled in appearance the cytoplasm of the cloudy, swollen epithelial cells lining the convoluted tubules. Lying around and between these cells was a homogeneous coagulum.

Tryptophan.—One gram of tryptophan will dissolve in 20 c.c. of physiologic sodium chlorid solution as the result of prolonged heating, but subsequent cooling to body temperature is quickly followed by precipitation. Attempts to inject solutions of the foregoing concentration fail because the needle soon becomes plugged with crystals. When 40 c.c. of salt solution is allowed for each gram of the amino-acid, little or no trouble from precipitation is encountered. A dilution varying from 30 to 45 c.c. of salt solution for each gram of the amino-acid was used in the experiments summarized in Table 11. The resulting solution was neutral to phenol red.

Examination of Table 11 leads to the impression that the kidneys of dogs are more easily damaged by tryptophan than those of the rabbit; but more experiments are needed definitely to answer this suggestion.

The five dog experiments were very satisfactory since they displayed a steady increase in the extent of the injury proportional to the increasing size of the dose. The injection of 0.5 gm. per kilogram caused no general or local disturbance; but the animals that received 2.0 gm. per

TABLE 11.—*Tryptophan*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Rabbit 44.....	1,450	0.6 (1) once	Urine remained normal until 48 hours after injection, when a little albumin and a few casts were found; the next specimen was again normal	No necropsy	
Rabbit 43.....	1,750	1.1 (2) once	Negative before injection; urine collected during 20 hours following injection nearly black (melanin ?), and showed heavy albuminuria and many granular casts	No histologic examination of kidney	Found dead 20 hours after injection; left lung congested but air containing
Rabbit 46.....	1,550	1.2 (1.8) once	Urine remained normal during the 48 hours following injection	No necropsy	
Dog 47 H.....	4,300	0.5 (2.15) once	Four specimens before and three after injection were all normal	No necropsy	
Dog 54 K.....	2,600	0.85 (2.2) once	Two specimens before injection, negative; 24 hours after injection, urine contained a little albumin and a few casts; thereafter, it was normal	No histologic abnormalities seen	Killed third day after injection
Dog 44 G.....	3,350	1 (3.5) once	Two specimens before injection, negative; specimens 24 and 48 hours after injection showed many granular casts and renal tubule cells	The lining cells of the convoluted tubules took stain irregularly and many nuclei were pycnotic; many casts in tubules	Killed 48 hours after injection
Dog 32.....	1,950	2 (4) once	No urine voided after injection; bladder empty at necropsy	Widespread simple necrosis of convoluted tubular epithelium; many casts (Fig. 2)	Animal in coma the morning after injection; killed
Dog 43 G.....	2,850	2 (5.7) once	Two specimens before injection, normal; anuric for 36 hours following injection; urine found in bladder at necropsy contained enormous numbers of granular casts	Figure 2, Experiment 4.....	Refused food for 36 hours after injection; killed 45 hours after injection
			Experiment Not Acceptable		
Rabbit 45.....	1,900	1 (2) once	Hematuria following injection.....	.....	Killed 24 hours after injection; ecchymoses of bladder mucosa explain bleeding

* Figure in parenthesis is total single dose.

kilogram suffered from a serious general intoxication, and a massive destruction of the renal tubules occurred in as short a time as thirty hours (Dog 32).

The protocol of Dog 43 G and Figure 2 give the details of an experiment in which a dog received a single injection of 2 gm. per kilogram.

EXPERIMENT 4.—The urine of Dog 43 G, a puppy, contained no albumin and no casts, April 27 and 28, 1924. The dog weighed 5,600 gm.

April 28, at 2 p. m., morphin sulphate, three-fourths grain (0.04 gm), was injected subcutaneously. About one hour later, we began the injection of a solution of tryptophan made by dissolving 5.7 gm. of tryptophan in 230 c.c. of physiologic sodium chlorid solution on a water bath at a temperature of from 38 to 40 degrees C. The injection took forty-five minutes and ended at 3:45 p. m.

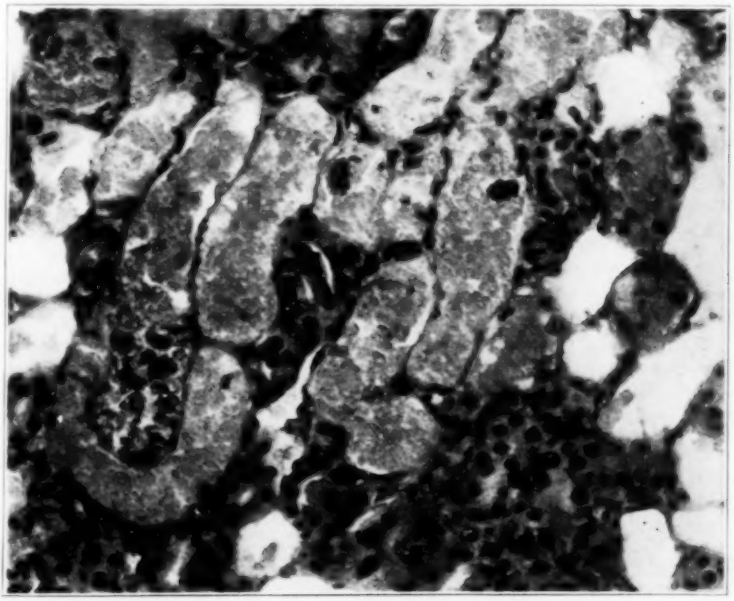

Fig. 2.—Widespread necrosis of the renal tubules produced by intravenous injection of tryptophan into a dog.

The morning of April 29 the dog looked sick; he lay on the bottom of the cage and refused food. No urine had been voided during the night.

April 30, the dog was still sick, and had not moved about. The morning urine was contaminated. At noon he was killed by a blow on the head.

Necropsy.—The kidneys weighed 30 gm. The capsule stripped easily leaving a smooth surface, gray in color, except for the presence of several ecchymotic patches. The section surface was gray, moist and lacking in markings, except those made by the arteries of the cortex. Several of the ecchymotic patches extended deep into the cortex. The latter appeared to be wider than normal.

The other organs presented no gross abnormalities. The urine contained in the bladder was free of albumin, but the sediment contained an enormous number of granular and cellular casts, and desquamated tubular epithelium.

Microscopic examination of the kidney showed that the majority of the cortical tubules had been severely injured. The nuclei of the lining cells of such tubules had either entirely disappeared, or had, in a few cells, been changed into smooth, structureless, deeply stained points. The cells in most of the cortical tubules had lost their margins, had become detached from the basement membrane, and lay free in the lumina as homogeneous, compact, smooth, deeply stained bodies (casts), or as paler, coalescing, granular droplets crowded together in the lumen. Some of the tubules, entirely denuded of epithelial lining, were empty. The glomeruli showed no injury. As one passed into the medulla, the cellular injury became less marked. The tubules of the medulla appeared to be normal, but contained many casts and desquamated epitheliums. The picture was that of widespread necrosis of the convoluted tubules.

Cystin.—This went into solution when 8.2 c.c. of normal sodium hydroxid was used for each gram. The resulting solution was slightly alkaline to phenol red. Evidence has already been presented in the section devoted to tyrosin which shows that the alkalinity of the solution could not be held responsible for the interesting renal injury produced by cystin. Further evidence of the truth of this statement is obtained by an examination of the data from Dog 28 E.

Experiment 5.—Dog 28 E, weighing 4,000 gm., received an intravenous injection of 33.6 c.c. of normal sodium hydroxid diluted to a volume of 100 c.c. with salt solution, February 14. The urine collected from the time of the injection to 9 a. m., February 15, contained no albumin and no casts. A second specimen of urine obtained the afternoon of February 15 and the urine voided the morning of February 16 failed to show either albumin or casts.

February 18, at 3:30 p. m., the dog received an intravenous injection of 4 gm. of cystin dissolved with 33 c.c. of normal sodium hydroxid and diluted to a volume of 100 c.c. with physiologic sodium chlorid solution.

February 19, at 5 p. m., the dog passed urine that contained an abundance of cellular casts and desquamated renal tubule cells. Albumin tests were negative. Urine collected during the morning of February 20 contained many cellular and granular casts and large granular cells but no albumin.

February 22, similar urine was obtained. February 25, the urine was again normal.

Examination of Table 12 shows that a single injection of 0.5 gm. per kilogram of cystin will produce evidence of renal injury.

The effect of somewhat larger doses is described in detail in the protocol of Dog 31 E. Figure 3 shows the character of the lesion in the renal tubules.

Experiment 6.—Dog 31 E, a puppy weighing 4,400 gm., was used. The urines of March 1 and 3, 1924, contained neither albumin nor casts.

March 3, at 3:30 p. m., the dog was given a subcutaneous injection of morphin sulphate, one-half grain (0.03 gm.). At 4:30 p. m. 3.5 gm. of cystin dissolved in 29 c.c. of normal sodium hydroxid and brought up to a volume of 75 c.c. with physiologic sodium chlorid solution was allowed to flow slowly into a vein previously exposed with aseptic precautions.

March 4, a flocculent precipitate formed in the boiled urine. It did not disappear on the addition of dilute acid. The cold urine to which dilute acetic acid was added also yielded a heavy precipitate. It was thought that this latter precipitate was cystin. Acetic acid was accordingly added to a portion of the urine until the filtrate remained clear on the addition of acid. This filtrate gave strongly positive tests for albumin. The sediment contained many desquamated epithelial cells, cellular and granular casts.

March 5, the urine gave less marked tests for albumin. The sediment was similar to that of the previous day.

March 7, 8 and 10, numerous cellular, granular and hyaline casts were seen in each specimen of urine.

March 12 and 13, the urine was albumin free, and no casts were seen.

March 14, the dog weighed 6,500 gm. Cystin, 6.5 gm., prepared as on March 3, was allowed to flow slowly into a vein about one hour after the dog had received morphin sulphate, three-fourths gram, subcutaneously.

March 15 and 16, in addition to albuminuria many epithelial cells, large cellular, granular and hyaline casts were present in both specimens.

March 16, at 3:30 p. m., the dog was killed by a blow on the head. At necropsy the kidneys weighed 78 gm. When the capsule was stripped off a pale yellow ground over which were strewn red points singly and in groups and irregular red patches was disclosed. Toward the hilum of one kidney a broad patch of cyanotic discoloration was seen. The section surface presented the same variegated appearance. No markings but the straight arteries were seen in the cortex. The other organs appeared normal.

Microscopic examination of the cortex of the kidney revealed many small areas that stood out sharply because of the lavender-blue presented by the irregular groups of structureless, smooth droplets occupying the space of a tubule. Higher magnification showed that such areas consisted of a section of tubule in which the epithelial cells had disappeared as such and had been changed into dead protoplasm impregnated with calcium salts. In some of these tubules a transition could be seen from fairly normal cells at one end through cells whose nuclei were greatly swollen, lacking in chromatin, and sometimes were represented by only a blue ring and whose cytoplasm was stained pale blue, to masses that had lost all resemblance to cells and had entirely replaced the tubular structure in the places where they occurred. Such areas of calcification were being surrounded by fibroblastic cells often several layers deep. Many tubules showed the earlier stages of this process but their epithelial cells had not yet lost their nuclei. Other tubules were stained a deep pink and consisted of cells with pale nuclei and granular, swollen cytoplasm. Desquamated cells and casts were numerous. In a few lumina small clumps of red blood cells were seen. The glomeruli were engorged and appeared to contain more nuclei than normal. The medulla presented no definite abnormalities.

It is an interesting question whether the renal injury caused by the intravenous injection of cystin and some of the other amino-acids would also occur if they entered the body through the liver, where they might be changed into nontoxic substances, or whence they might be slowly distributed in dilutions so great as to be innocuous. A single experiment gave us a clear answer to this question regarding cystin. The data obtained from Dog 39 F, Table 13, showed that the injection of 1 gm. of cystin per kilogram into a tributary of the portal vein was followed by the urinary signs of renal injury.

TABLE 12.—*Cystin*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Dog 60 K.....	5,200	0.5 (2.6) every other day; three injections	Two specimens before injection, negative; a few casts seen day after first injection; they gradually increased until they were "frequent" after third injection	No histologic abnormalities of kidney seen	Killed 45 hours after last injection
Dog 29 E.....	3,270	0.5 (1.65) every third day; five injections	Two specimens before injection, negative; after second injection, a few granular and hyaline casts found at every examination	Right kidney: epithelium of convoluted tubules overstained, swollen and hazy; in a few tubules the cells had lost their nuclei and the cytoplasm was represented by pale droplets filling the lumen	Killed 48 hours after last injection; left kidney presented the picture of congenital hydronephrosis
Dog 38.....	1,750	1 (1.75) once	Two specimens before injection, negative; specimen day after injection, negative	Proximal convoluted tubules show moderate cloudy swelling; no casts	Killed 30 hours after injection
Dog 28 E.....	4,000	Note: 33.6 c.c. of normal sodium hydroxid brought up to 100 c.c. volume with salt solution; four days later, 1 (4) cystin plus 33.6 c.c. of normal sodium hydroxid brought up to 100 c.c. volume with salt solution; eight days later, cystin injection repeated	Three specimens before injection, negative; three specimens following injection of alkali, negative; 48 hours after first injection of cystin many granular and cellular casts seen; seven days after this injection, urine again normal; findings after second injection of cystin not significant because of the pneumonia	Histologic abnormalities not significant because of pneumonia	Ill 48 hours after second injection of cystin; killed; necropsy diagnosis, pneumonia
Dog 31 E.....	4,400 at time of first injection; 6,500 at time of second injection	0.8 (3.3) once; eleven days later, 1 (6.5) once	Two specimens before injection, negative; many casts and tubule cells found day after first injection; present daily for ten days; absent day after second injection; thereafter, present to death	Experiment 6, Figure 3.....	Killed 48 hours after second injection

Dog 37.....	1,150	1 (1.15), two injections with interval of six days	Two specimens before injection, negative; 48 hours after first injection, the urine contained much albumin, many granular and some hyaline casts; 48 hours after second injection, the urine showed similar abnormalities	Convoluted tubules stood out distinctly because they were stained a much deeper pink than rest of tissue; epithelial cells of these tubules showed signs of degeneration: swelling, loss of outline, vacuolation, pycnosis and disappearance of nuclei, but no calcification seen; glomeruli apparently normal; casts very numerous	Killed 48 hours after second injection
Dog 24 C.....	2,650	1 (2.65), two injections with interval of six days	Three specimens before injection, negative; five hours after first injection, albumin and many granular and hyaline casts found; 24 hours after first injection, sediment contained enormous numbers of large granular mononuclear cells and many casts showing all transitions from a series of several epithelial cells, whose borders were still plainly seen, to typical granular casts; similar urinary abnormalities were noted thereafter until death	Microscopic picture same as that described in protocol of Dog 31 E and illustrated by Figure 3	Killed 24 hours after second injection
Dog 27 D.....	2,750	2 (5.5), two injections with interval of nine days	Two specimens before injection, negative; 24 hours after injection, no casts; 72 hours after injection, many granular and some cellular casts; similar sediment found regularly thereafter	Histologic changes of same type as those found in the kidneys of Dogs 24 C and 31 E but more extensive; many more tubules showed advanced degenerative changes; while calcification was marked, it had taken place in only a minority of the injured tubules; broad patches of hemorrhage seen in upper medulla; extreme congestion seen everywhere	Died 6 hours after second injection; necropsy: all organs engorged; scattered irregularly over peritoneal surfaces were white flecks easily picked up in form of dry, curdlike material; pleural surfaces presented same features; when capsule of kidney was stripped off, dull red background was seen over which minute white points were dusted; on section, curdlike material was found in renal pelvis; veins stood out as broad black bands; collecting tubules in medulla were visible as intense white streaks; cortical tissue was streaked by fine white lines
			Experiments Not Acceptable		
Dog 35.....	1,750	0.28 (0.5) once	Urine remained normal during 48 hours following injection	.....	Five days after injection, discontinued because of diarrhea
Dog 34.....	2,800	1 (2.8) once	Two specimens before injection, negative.....	.....	Died 48 hours after injection; necropsy revealed extensive pneumonia

* Figure in parenthesis is total single dose.

Dog 40 F received the same treatment as its litter mate, Dog 39 F, except that the solution injected into the former contained no cystin. The continued absence of casts and other abnormalities from the urine of Dog 40 F after the injection proves that neither the anesthetic nor the technic of the operation can be held responsible for the signs of kidney injury which followed the injection of cystin into a portal tributary of Dog 39 F.

CONTROLS

The experimental procedure used in these studies was so simple that the chance of error inherent in the employment of elaborate appa-

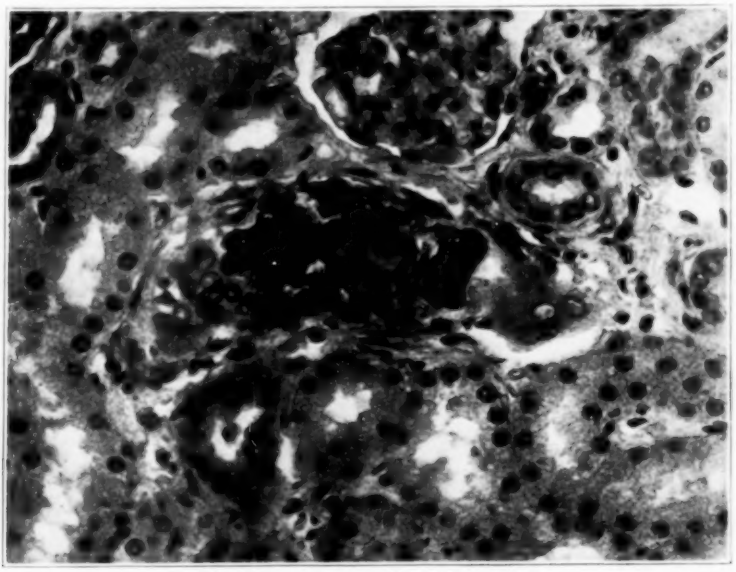

Fig. 3.—Necrosis and deposition of calcium salts in some of the dead cells following the intravenous injection of cystin into a dog.

ratus and complicated technic was almost negligible. The safety of the intravenous route has been so thoroughly established by its very extensive use both clinically and experimentally that disturbances following this method of administration are confidently attributed to the injected substance and not to the technic. Nevertheless, it is desirable to control this procedure as used by us. The danger of error, if any, lies in the bulk of the solution and its reaction, in struggling on the part of the animal, in the anesthetic used to avoid it, and finally in infection of the injection site.

That none of these things was the cause of the renal damage in the case of the amino-acids that we have concluded are nephrotoxic is proved by the uniformly negative results obtained with alanin, leucin, glycin, phenylalanin and glutamic acid. For example, the dog that was given leucin so diluted that he received 82 c.c. of fluid per kilogram manifested no subsequent renal disturbance. Likewise, large amounts of alkali were required for the neutralization of glutamic acid and the latter was given to Dog 57 K with 48 c.c. of combined standard sodium hydroxid, or more than 14 c.c. per kilogram, without renal damage (glutamic acid section). Even more impressive is the experience with Dog 25 D (Table 7), who received a total of 193.6 c.c. of standard sodium hydroxid in six days, used to neutralize aspartic acid, and who continued to void normal urine. In the case of these amino-acids, the alkali was used to neutralize the acidity of the dissolved amino-acid, but tyrosin and cystin require the solution to be slightly alkaline to maintain solubility; hence the negative results obtained with the large amount of alkali injected as a part of a neutral solution do not completely control possible renal injury from the alkaline quality of solutions of tyrosin and cystin. It has been pointed out that in the case of tyrosin the alkalinity amounted to only two thousand five hundredth normal (Table 9). The cystin solution was of the same order of alkalinity. Furthermore, the administration of 34 c.c. of free standard sodium hydroxid twice to one dog (tyrosin section) and 33.6 c.c. of free sodium hydroxid to another dog (cystin section) was not followed by any evidence of renal damage. Since these large amounts of free alkali had no harmful effect on the kidneys, it is evident that the nephrotoxicity of the solutions of tyrosin and cystin is solely attributable to the dissolved amino-acid.

Violent struggling is known to produce albumin and casts in the urine. The rabbits offered no resistance to the injections. Struggling was satisfactorily prevented in the dogs by the use of morphin. It is clear that this drug does not damage the kidneys because of the negative results following its use in the case of the five amino-acids already mentioned, and in the control experiments with alkali.

Infection at the site of administration never occurred in rabbits because there was incision. In the dogs the wounds nearly always healed normally. In a few instances the wounds did not heal by first intention, but the largest sloughs occurred in the animals that received the free alkali.

It might be thought that the excretion of the large amount of urea formed from the injected amino-acids caused the signs of renal injury noted by us. That this is not an adequate explanation is shown by the fact that some amino-acids did not injure the kidneys. It will be recalled that the innocuous amino-acids are, in general, those of smaller

TABLE 13.—*Injection of Cystin into a Mesenteric Vein*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine	Histology	Remarks
Dog 39 F.....	3,900	1 (3.9) once neutralized with 32 c.c. of normal sodium hydroxid and made up to volume of 100 c.c. with salt solution	Two specimens before injection, negative; 20 hours after injection, no casts or red blood cells; 24 hours after injection, several large granular casts and some red blood cells found; 40 hours after injection, numerous granular casts and occasional red blood cells seen	Epithelium of convoluted tubules showed moderate cloudy swelling; typical casts numerous	Ether used for anesthesia; good recovery; killed 48 hours after operation; operation site clean
Dog 40 F.....	3,700	100 c.c. of salt solution	Two specimens before injection, negative; two specimens following injection, negative	No histologic abnormalities of kidney	Ether used for anesthesia; good recovery; killed 48 hours after operation; no signs of infection

* Figure in parenthesis is total single dose.

molecular weight; and that they therefore actually yielded more urea gram for gram than the nephrotoxic amino-acids. The injections of urea given in Table 14 afford clear evidence that it is not damaging to the kidneys.

COMMENT

The intravenous administration of alanin, leucin, glycin, phenylalanin and glutamic acid gave us no evidence of renal injury in doses as large as 2 gm. per kilogram. Arginin and aspartic acid are mildly nephrotoxic, while serious kidney damage was produced by lysin, histidin, tyrosin, tryptophan and cystin. We have been unable to obtain serin or prolin.

The most important outcome of these studies is the demonstration that normal digestion products of protein are a source of renal injury under the conditions of these experiments.

TABLE 14.—*Urea*

Animal	Weight, Gm.	Dose per Kilogram,* Gm.	Urine
Rabbit 25	2,500	2 (5) dissolved in 30 c.c. of salt solution	Urine normal before injection; 24 hours after injection, catheter specimen contained no albumin; 60 hours after injection, catheter specimen contained no albumin
Rabbit 27	2,200	2.3 (5) dissolved in 20 c.c. of physiologic sodium chlorid solution	Two specimens before injection, negative; 4 hours after injection, urine normal; 24 hours after injection, urine contained no albumin and no casts
Rabbit 28	1,850	2.8 (5) dissolved in 20 c.c. of physiologic sodium chlorid solution	Two specimens before injection, negative; 24 hours after injection, urine contained neither albumin nor casts; 48 hours after injection, urine contained neither albumin nor casts; 60 hours after injection, urine contained neither albumin nor casts

* Figure in parenthesis is total single dose.

It will be recalled that this investigation was undertaken in an attempt to explain the renal damage from high protein diets, since such diets increase the absorption into the blood stream of amino-acids. The concentration of nephrotoxic amino-acids following a high protein meal probably does not reach that caused by our injections. The same thing is true of the amino-acids and their metabolites in the urine. But it is also in general true that repeated doses of a poison, each too small to cause demonstrable injury, will eventually result in serious damage. May there not be a similar relationship between the chronic nephropathy from high protein diets and the acute injury following the injection of amino-acids? We have noted in the case of some amino-acids that single doses that were too small to give evidence of injury would cause the appearance of abnormal urine, if repeated only a few times. Furthermore, we do not know how small a dose of injected amino-acid will

cause injury. The crudity of the methods for detecting such injury precludes the possibility of demonstrating it in lesser degrees. This difficulty became very evident to us when we found that it requires about twice as much amino-acid to give unequivocal histologic evidence of renal damage as is needed to produce cylindruria. The smallest doses with which we obtained abnormalities are given in Table 15.

The amino-acids normally enter the body from the digestive tract; hence it may properly be questioned whether information obtained by intravenous injection has any bearing on effects attributed to excesses arriving through normal channels. A certain amount of information tending to answer this question is available. Our injection of cystin into the portal vein of Dog 39 F shows that the injury is not prevented by passage of the amino-acid through the liver. In certain investigations of the metabolism of cystin, H. B. Lewis[8] (1925) has noted that the ingestion of cystin by rabbits is followed by serious kidney damage.

TABLE 15.—*Smallest Dose of Amino-Acid that Produced Renal Injury*

Amino-Acid	Rabbits, Gm. per Kg.	Dogs, Gm. per Kg.
Arginin	1.0	...
Aspartic acid	0.5	2.0 (?)
Lysin	0.15	0.6
Histidin	0.10	0.33
Tyrosin	0.23	1.0
Tryptophan	0.6	0.85
Cystin	...	0.5

Finally, experiments still incomplete being conducted by A. C. Curtis have shown that the addition of cystin to standard diets causes renal injury in rats.

It is also of interest to note the difference in the reactions of the kidneys of rabbits and of dogs to some of the amino-acids. These differences are to be seen in Table 15.

Sufficient information is not at hand to assign a place to these new data in the problem of the etiology of chronic nephritis in man. The difficulty is in part due to the difference in reactions of different species to the amino-acids; and in part to the difference in the histologic picture produced by the amino-acids and that found in the human cases. Nevertheless, the fact remains that certain amino-acids are capable of producing serious injury of the kidney. Unless future investigators show that this fact is irrelevant, it must be included in any attempt to formulate a comprehensive picture of the etiology of human nephritis.

8. Lewis, H. B.: J. Biol. Chem. **63**:20, 1925.

In this connection it is of interest to mention that Folin and Berglund [9] (1924) have found another normal product of protein metabolism that causes serious renal disease. In the course of their studies of uric acid metabolism they found that the intravenous injection of uric acid was attended by evidence of renal injury.

SUMMARY

It has been demonstrated that the amino-acids, arginin, aspartic acid, lysin, histidin, tyrosin, tryptophan and cystin are nephrotoxic.

9. Folin, O.; Berglund, H., and Derick, C.: J. Biol. Chem. **60**:301 (June) 1924.

THE AURICULAR WAVE (P) OF THE ELECTROCARDIOGRAM

CLINICAL OBSERVATIONS WITH ESPECIAL REFERENCE TO PULMONIC AND MITRAL STENOSES

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LITERATURE

Studies concerning the diagnostic significance of changes in the auricular or P wave of the electrocardiogram have not been numerous. Increase in height and prolongation of the wave, occurring most often in mitral stenosis, have been noted by Einthoven,[1] Kraus and Nicolai[2] and Samojloff;[3] Goddard[4] assumed a more or less definite quantitative relationship to exist between such augmentation of the P wave and auricular hypertrophy. He considered as increased all P waves when they were greater than T in the same curve, that is $\frac{P}{T} = 1+$. Checking this relationship, he found that there was some relative increase in height (of the P wave) in 54 per cent. of the cases of mitral disease studied. However, in five cases that came to necropsy, one with very slight hypertrophy of the auricle showed marked exaggeration of the P wave while another with decided hypertrophy showed only a slight relative alteration of the P. On the other hand a check of all the exaggerated P waves against the histories of the patients showed that 45 per cent. had mitral disease and that a small percentage had clinically normal hearts. Goddard then concludes that the association of P wave exaggeration with auricular hypertrophy, though suggestive, is not a constant one.

Experiments seeking to determine the nature and source of the P wave by Samojloff,[5] Kraus and Nicolai,[6] Lewis, Meakins and White;[7]

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1. Einthoven, W.: Le Telecardiogramme, Arch. internat. de physiol. **4**:148, 1906-1907.
2. Kraus, F., and Nicolai, G. F.: Berl. klin. Wchnschr. **44**:812, 1907.
3. Samojloff, A.: München. med. Wchnschr. **56**:1943, 1909.
4. Goddard, C. H.: Arch. Int. Med. **16**:633 (Oct.) 1915.
5. Samojloff, A.: Festschrift Herman, 1908, p. 171.
6. Kraus, F., and Nicolai, G. F.: Das Elektrokardiogramm des Gesunden und Kranken Menschen, Leipzig, 1910.
7. Lewis, T.; Meakins, J., and White, P. D.: Phil. Tr. Roy Soc. London, **205**:375, 1914.

and Eyster and Meek [8] have shown that it is a composite representation of the excitation wave as it spreads from the region of the sinus, the sino-auricular node, over the auricle. Recently, the interesting and fundamentally important work of Einthoven [9] has shown that the electrical and mechanical expressions of muscular activity are synchronous and parallel in degree. This applies to heart muscle as well as to skeletal muscle. The myocardiogram if accurately obtained corresponds exactly with the electrocardiogram in time of onset, duration and force. Thus the auricular or P wave of the electrocardiogram does not represent simply the brief early expression of the excitatory process in the auricle but in fact the entire auricular contraction. Instead of measuring in time only one third of the duration of auricular action it really coincides with it. The T wave of the auricle—the so-called Ta wave of the electrocardiogram—had been pointed out years ago by several observers but it has now been correlated to auricular systole by Einthoven.[9] Sprague and White [10] have recently shown the frequent clinical occurrence of this Ta wave of the electrocardiogram. Thus, the larger and more active the auricles, the larger and longer should be the auricular deflections of the electrocardiogram.

Attention has also been called to the influence of the position of the heart in the body, as determined by respiration or other factors, and of the periodic shift of the pacemaker within the node, as shown by Lewis, Meakins and White.[8]

Finally, the influence of the extrinsic cardiac nerves on the P wave has been studied. Einthoven [11] demonstrated that simple section of the vagus in dogs produced a marked rise in the P wave. In such an experiment of course changes in the auricle could play no rôle. Rothberger and Winterberg [12] repeated and confirmed this, and further showed that section of the cardiac accelerators (increased vagus effect) was followed by a pronounced decrease in P. Selenin,[13] however, saw no such effect on the dog's heart in situ, following full therapeutic dosage of digitalis.

PRESENT INVESTIGATION

The reason for the present study was the desire to determine the significance of high P waves with reference to the diagnosis of pulmonic stenosis and mitral stenosis.

8. Eyster, J. A. E., and Meek, W. J.: Arch. Int. Med. **11**:204 (Feb.) 1913.
9. Einthoven, W.: Goddard Lectures, Harvard Medical School, 1924.
10. Sprague, H. B., and White, P. D.: J. Clin. Invest. **1**:389 (April) 1925.
11. Einthoven, W.: Arch. f. d. ges. Physiol. **122**:537, 1908.
12. Rothberger, J., and Winterberg, H.: Arch. f. d. ges. Physiol. **135**:506, 1910.
13. Selenin, W. P.: Arch. f. d. ges. Physiol. **143**:137, 1912.

The study has included three distinct parts as follows: First, the analysis of (*a*) the amplitude of the P wave, (*b*) the values of angle and index of electrical axis deviation, and (*c*) the clinical diagnosis in 132 unselected cases seen at the Massachusetts General Hospital from 1914 to 1924 in whom electrocardiograms showed an amplitude of P in Lead I greater than 0.1 millivolt (1 mm.), or of P in Lead II equal to or greater than 0.3 millivolt (3 mm.). Second, a similar analysis of all cases definitely diagnosed pulmonic stenosis and coming to electro-

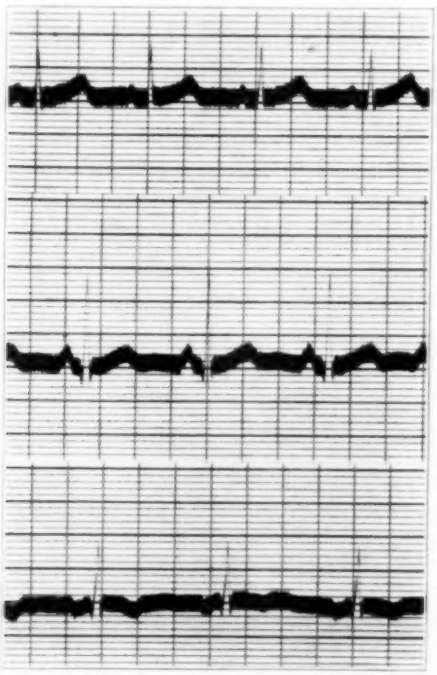

Fig. 1.—Leads I, II and III, normal, for comparison with Figures 2 and 3; time, 0.2 second; potential, 10^{-4} volts per millimeter.

cardiographic study at the Massachusetts General Hospital from 1914 to 1924. Third, the same study of 100 unselected cases of "pure" mitral stenosis electrocardiographed at the Massachusetts General Hospital.

The height of the P wave has been studied rather than its length or duration for several reasons: First, it is more evident and more easily measured; second, the occurrence of the T wave of the auricle, the so-called Ta wave, sometimes appearing as a direct prolongation

of the P wave, makes it difficult to determine the limits of the P, and third, the height of the P wave may be abnormally increased with little if any increase in duration while the reverse is rarely true. Almost invariably if the P is longer than normal it is also higher than normal in either Lead I, Lead II, or both. For example, out of the fifty-eight cases of mitral stenosis with normal rhythm (listed in Table 7) only nine failed to show high P waves in either Lead I or Lead II and none of these nine showed any abnormal length of the P waves; incidentally, the P wave in Lead III was low in all of these nine cases.

Rarely if ever is the P wave in Lead III as large as in the other leads; usually it is of very low potential, either upright, inverted or iso-electric. Thus P_3 has not been included in the present analysis because of its unimportance.

With the abnormal increase in height of the P waves in Lead I and Lead II there is often abnormal notching in addition to increased length. A duration of the P wave (not including the Ta wave) beyond 0.1 second in any lead and a height above 1 mm. (0.1 millivolt) in Lead I, or a height equal to or above 3 mm. (0.3 millivolt) in Lead II, we have considered abnormal.

The formula used for determining the index was that outlined by White and Bock[14] and the angles were arrived at by the use of the triangle of Einthoven, following the method described by Carter, Richter and Greene.[15] By the index method figures of -12 or more negative indicate abnormal right axis deviation, and of $+20$ or more positive abnormal left axis deviation; -12 to $+20$ are within normal limits. By the angle method figures beyond $+90$ degrees represent abnormal right axis deviation and on the negative (upper) side of 0 degrees abnormal left axis deviation; 0 to $+90$ degrees (the right lower quadrant) are within normal limits.

PART I

Tables 1, 2, 3, 4, 5 and 6 include the cases examined in the first part of the study. The clinical diagnosis has determined the inclusion of the various cases under one or another of these tables, wherein pulmonic stenosis, mitral stenosis pure, and mitral stenosis with other valve defects are each given separately, while other diagnoses encountered are embodied in Table 6.

Examination of Tables 2, 3, 4 and 5 shows that the amplitude of P_2 was equal to or greater than 3 mm. in 68 per cent. of all of the seventy-two cases of mitral stenosis encountered, and an interesting

14. White, P. D., and Bock, A. V.: Am. J. M. Sc. **156**:17 (July) 1918.
15. Carter, E. P.; Richter, C. P., and Greene, C. H.: Bull. Johns Hopkins Hosp. **30**:162 (June) 1919.

TABLE 1.—*Pulmonic Stenosis* *

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
6413	—20	150	2.5	4
7465	—30	90	1	5
6838	—34	125	2	4
1994	—12	165	1.8	3.8
7919	—42	159	4	4
745	—43	143	1.5	1.2
3940	—18	112	2	2.5
6448	—36	134	2	3
5805	—28	150	2	4.5
974	—25	140	2	2.5
4057	—23	142	2.5	3
6573	—32	132	1	3
7465	—30	90	1	5
7438	—24	118	2	3.5
5879	—30	143	1.7	4
7050	—18	149	2	2.5
6500	—28	118	2	3
8870	—16	116	1.5	4
6448	—36	134	3	4
8068	—29	118	0.5	6

* Values throughout these tables are positive unless otherwise noted.

Summary: Total cases, nineteen (twenty plates). Sixteen cases had an amplitude of P_2 equal to or greater than 3 mm. The other three cases had an amplitude of P_1 greater than 1 mm. Eighteen had an index below —15. One had an index of —12. All had angles of 90 degrees or more.

TABLE 2.—*Mitral Stenosis (Pure)* *

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
906	—15	120	2	3
1917	—11	69	2	2
2209	—17	102	2	2
2275	—15	130	1.8	2
1605	—8.5	81	1.5	2.7
3096	—13	95	1	4
2552	—19.5	120	2.2	2.2
2562	2	56	1.5	3.5
0633	—1	59	2	3
0685	—20	90	1	3
6675	—1	62	2	3.5
6801	—7	75	1.5	3.5
6774	—4.1	164	1	3
6895	—6	90	2.2	1.8
6879	—23	102	1.2	2.5
6969	—10	72	1.5	2
6948	5.5	25	2	4
8518	—12	98	2	5
7151	—5	69	1	4
6525	—10	90	3	3
6471	—16	117	2	4
7106	—6	76	1	5
6808	—30	112	1.5	5
1324	—13	121	1.6	2.5
2083	—10	78	1.5	3.2
6556	—30	122	2	2.5
5502	—32	122	2	2.5
8518	—12	98	2	5
6435	—9	68	2.5	4
7057	—11	99	2.5	5
6308	—3	67	2	3
6325	—23	98	2	2.5
6535	—13	99	2	3
6831	15	—18	1.5	3.5
6935	—9	108	2	2.5
7104	—13	92	2	2.5
5023	0	60	1.5	3
6253	—1	62	2	3
4476	2	43	2	3
4501	—9	73	2	2
7191	—31	118	3	2.5
1355	—21	122	2.5	4
1390	—19	105	3	2.5

* Among the cases with electrocardiograms showing high P waves these had been diagnosed as pure mitral stenosis.

Summary: Total cases, forty-three. Thirty-eight had an amplitude of P_1 greater than 1 mm. (88 per cent.); thirty-eight had an amplitude of P_2 greater than 2 mm. (88 per cent.), and twenty-seven had an amplitude of P_2 equal to or greater than 3 mm. (63 per cent.). Indexes varied from +15 to —41 (four had positive values). Fourteen had indexes of —15 or below (33 per cent.); twenty-five had indexes of —10 or below (58 per cent.), and twenty-five had angles of +90 degrees or more (58 per cent.).

TABLE 3.—*Mitral Stenosis and Regurgitation*

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
2173	−25	102	3	6
547	−25	127	2	5
948	−12	140	2	4
21	−22.5	96	2.5	5
332	−28.5	114	1	3
987	−18	112	1.5	2.1
1383	−25	107	1	3
1742	−14.5	88	1.5	2
2475	−32	109	3	2.5
3197	−6	86	1.5	1.3
4355	−21	132	2	2.5
4103	−3	66	2	3
50	−25	90	1.5	3.5
6689	−11	71	4	7

Summary: Total cases, fourteen. Twelve had an amplitude of P_1 greater than 1 mm. (85 per cent.); twelve had an amplitude of P_2 greater than 2 mm. (85 per cent.), and nine had an amplitude of P_2 equal to or greater than 3 mm. (64 per cent.). Nine had indexes below −15; twelve had indexes of −10 or below (85 per cent.), and ten had angles equal to or greater than +90 degrees (71 per cent.).

TABLE 4.—*Mitral Stenosis and Aortic Regurgitation*

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
270	−15	90	1.8	2.5
4170	−12	73	3.5	5.5
7182	10	−47	1	3
7786	5	53	1.5	3
8017	−10	90	1.5	3.5
2189	−11.5	76	1.3	3.3
4171	2	58	4	3
2419	19	−4	1.2	1.5
3026	−9	72	1	3
6647	42	−32	2	4

Summary: Total cases, ten. Eight had an amplitude of P_1 over 1 mm. (80 per cent.); nine had an amplitude of P_2 over 2 mm., and eight had an amplitude of P_2 of 3 mm. or over (80 per cent.). Two had an angle of only 90 degrees or over. Four cases only had indexes of −10 or below (40 per cent.), and one case only had an index of −15.

TABLE 5.—*Mitral Stenosis and Regurgitation and Aortic Stenosis and Regurgitation*

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
7682	−8	75	1.5	4
7721	−17	100	2	4.5
3974	0	62	3	5
3988	0.5	60	3	3
6800	−26	110	1.5	3.5

Summary: Total cases, five. All had amplitude of P_1 greater than 1 mm.; all had amplitude of P_2 of 3 mm. or over. All had angles of 60 degrees or over; two had angles of 90 degrees or over (40 per cent.), and two had indexes of −10 or below.

Summary of Tables 3, 4 and 5: Total cases, twenty-nine. Twenty-five had amplitude of P_1 greater than 1 mm. (86 per cent.); twenty-six had amplitude of P_2 equal to or over 2 mm., and twenty-two had amplitude of P_2 equal to or over 3 mm. (76 per cent.). Eighteen had indexes of −10 or below. Twenty-four had angles of 60 degrees or more, and fourteen had angles of 90 degrees or more (48 per cent.).

TABLE 6.—*Miscellaneous Conditions* *

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.	Clinical Diagnoses
4166	10	48	3	2	Arteriosclerosis; cerebral embolism; sino-auricular tachycardia
6148	—17	170	2	4	Effort syndrome; sino-auricular tachycardia
2057	—10	72	1	3	Arteriosclerosis; sino-auricular tachycardia
928	—15	123	1.5	2	Cardiac neurosis; sino-auricular tachycardia
809	0.5	61	1.6	5	Sino-auricular tachycardia
1313	—13	78	0.5	3	Pericarditis (?); mitral stenosis (?); sino-auricular tachycardia
1256	1	57	1.5	5	Goiter; toxemia of pregnancy; sino-auricular tachycardia
108	3	56	2.1	5	Nephritis; hypertension; arteriosclerosis
3295	—0.5	65	1.5	2	Nephritis; hypertension; arteriosclerosis; sino-auricular tachycardia
4358	5	83	2.5	2.5	Nephritis; hypertension; sino-auricular tachycardia
6410	19	23	2	4	Hypertension; congestive heart failure
6476	31	4	2.5	4	Hypertension; congestive heart failure; sino-auricular tachycardia
6691	1.5	59	1	6	Exophthalmic goiter; sino-auricular tachycardia
6716	0	54	1.5	4	Coronary sclerosis; sino-auricular tachycardia
6771	—27	110	1	4.5	Sino-auricular tachycardia
7001	14	5	2	1.5	Nephritis; hypertension; coronary sclerosis
7031	22	7	2	4	Hypertension; cardiac hypertrophy; arteriosclerosis
7042	45	35	1.5	3	Hypertension; arteriosclerosis; sino-auricular tachycardia
7162	—1	63	1	4.5	Essential hypertension
8281	19	30	2.1	4	Hypertension; arteriosclerosis; hemiplegia
7156	10	30	1	5	No disease
6575	—36	128	2	4	Mitral stenosis (?); sino-auricular tachycardia
6588	—11	73	1	4.6	Mitral stenosis (?); sino-auricular tachycardia
7063	9	28	1.5	2.5	Rheumatic history; normal heart
2954	—35	85	2	1	Arteriosclerotic and syphilitic heart; sino-auricular tachycardia
4654	—7	58	1.5	2	Perinephritic abscess; sino-auricular tachycardia
3854	—7	94	1	4	Hypertension; varicocele
5480	15	10	2	3.2	Chorea (?); mitral stenosis (?); sino-auricular tachycardia
5730	2	35	3	3	Nephritis; hypertension
1445	—8	75	2	3	Phthisis (?); mitral stenosis (?)
6820	—7	78	1	4	Mitral stenosis (?); sino-auricular tachycardia
6857	—8	100	2	2	Hypertension; uremia; prostatitis
6487	6	46	1	3	Nephritis; hypertension; sino-auricular tachycardia
7068	—2	65	2	4	Congenital heart (?); ventricular septal defect; sino-auricular tachycardia
7054	8	59	2	6.5	Congenital heart; septal defect; heart block
6500	—28	118	2	4	Congenital heart; septal defect; patent ductus arteriosus; sino-auricular tachycardia; pulmonic stenosis (?)
7170	—12	110	2	1	Congenital heart; ventricular septal defect (?); pulmonic stenosis (?); sino-auricular tachycardia
6459	—30	86	2.5	4	Congenital heart; pulmonic stenosis (?); sino-auricular tachycardia
8121	2	57	2	3.5	Nephritis; hypertension; uremia
8155	5	53	1.5	5	Nephritis; hypertension; uremia; sino-auricular tachycardia
8975	0	60	2.5	3	Sino-auricular tachycardia; curvature of spine

* All cases having other than definite pulmonic stenosis or mitral stenosis encountered in the review of cases with electrocardiograms showing high P waves.

Summary: Total cases, forty-one; doubtful mitral stenosis, six; doubtful pulmonic stenosis, three; probable interventricular septal defect without pulmonic stenosis, two; total congenital heart cases, five. Sino-auricular tachycardia (heart rate of 100 or more) without question of mitral stenosis or congenital heart defects, eighteen. Hypertension with or without nephritis, not included in foregoing listing, ten. Rheumatic history without evidence of heart disease, one, and no disease, one.

approximation was shown by the percentage of right axis deviation, in that 60 per cent. of all cases had indexes equal to or below — 10, and 54 per cent. had angles equal to or greater than 90 degrees.

A further interesting and expected finding in this series of combined mitral lesions (Tables 3, 4 and 5) is that the mechanism involved causes an increase in the amplitude of P but a decrease in the negativity of the indexes and in the positive angles (that is a lessened tendency to right axis deviation), as compared with the pure mitral stenosis cases.

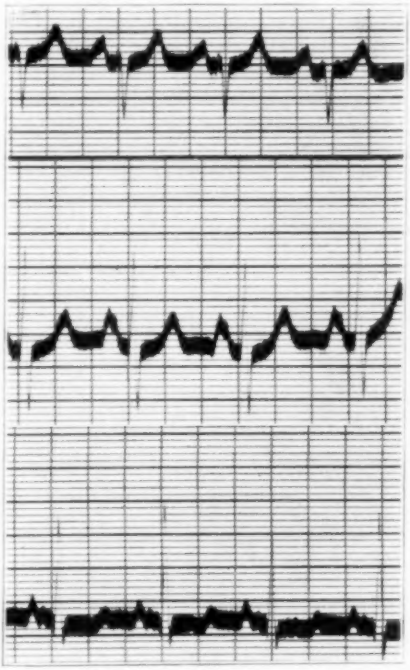

Fig. 2.—Leads I, II and III in well marked mitral stenosis; large P waves in Leads I and II and pronounced right axis deviation (right ventricular preponderance).

It is of much interest to note that twenty-nine of these forty-one miscellaneous cases (Table 6) showed conditions that could easily explain the abnormally high P waves. Mitral stenosis and pulmonic stenosis were probably present in the cases listed doubtful though the signs were not well enough marked to make a positive diagnosis. There were two other cases of congenital heart disease showing large P waves probably with interventricular defects; it is likely that the auri-

cles as well as the ventricles in some patients of this type are overworked with resultant hypertrophy or increased activity. Sino-auricular tachycardia is usually the result of sympathetic nerve stimulation, and it is a well recognized fact physiologically that such stimulation may result in increase in amplitude of the auricular deflection (and also of the T wave) of the electrocardiogram. The frequent finding of hypertension in some of the cases with high P waves may be significant—here again there is a possibility that the auricles as well as the ventricles

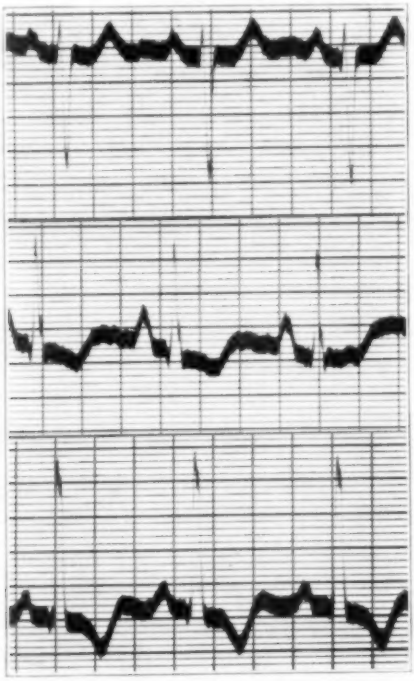

Fig. 3.—Leads I, II and III in congenital pulmonic stenosis; large P waves in Leads I and II and marked right axis deviation.

may be overworked with resultant evidence of this increased activity, although large P waves are not the usual finding in hypertension. Only two of the whole group of the forty-one miscellaneous cases, and in fact only two of the entire series of 132 cases showing high P waves, remain unexplained in the presence of definite or doubtful mitral stenosis, definite or doubtful pulmonic stenosis, other congenital heart defects, sino-auricular tachycardia, or the possible influence of hypertension.

PART II

When we came to undertake the second part of the study mentioned above, that is, an analysis of the P waves as to their amplitude and of the angles and indexes in all cases of definite pulmonic stenosis in which electrocardiograms were made at the Massachusetts General Hospital since 1914, we discovered, as has previously been mentioned, that as a result of their increase in the amplitude of P they were all covered by Table 1, and had therefore all been analyzed. Seventy-nine per cent. of all these cases showed an amplitude of P_2 equal to or greater than 3 mm. Seventy-nine per cent. had an amplitude of P_1 greater than 1 mm., and 100 per cent. had definite right axis deviation with angles of over 90 degrees and indexes of — 10 or below. All cases had either P_1 over 1 mm. or P_2 over or equal to 3 mm.

PART III

Turning to the third study mentioned we examined the plates of 100 unselected cases that had been diagnosed clinically as pure mitral stenosis (Table 7).

It is evident from Table 7 that in this series, 45 per cent. of those showing P waves (that is, without fibrillation) had an amplitude of P_2 equal to or greater than 3 mm., and 78 per cent. had an amplitude of P_1 greater than 1 mm., whereas 84 per cent. had P_1 or P_2 equaling these high figures. Furthermore, one half of these cases showed the angles and indexes of right axis deviation. With regard to the angles in the entire series (with or without fibrillation) they were found to equal or exceed 90 degrees in 47 per cent. of all cases, while the indexes in the total series were equal to or less than — 10 in 52 per cent. of the cases.

SUMMARY AND CONCLUSIONS

1. A study has been made of all the patients (132) who have shown by electrocardiogram during nine and one-half years at the Massachusetts General Hospital auricular or P waves greater than 0.1 millivolt (1 mm.) in amplitude in Lead I or equal to or greater than 0.3 millivolt (3 mm.) in Lead II. Of these cases nineteen (14 per cent.) had definite congenital pulmonic stenosis; three (2 per cent.) had doubtful congenital pulmonic stenosis; seventy-two (55 per cent.) had definite mitral stenosis; six (5 per cent.) had doubtful mitral stenosis; two (2 per cent.) had probable interventricular septal defect, and eighteen (14 per cent.) had sino-auricular tachycardia without question of mitral stenosis or congenital heart defects—a total of 120, or 91 per cent. of the 132 cases. Only twelve cases (9 per cent.) are not readily accounted for. Ten of these (8 per cent.) had hypertension with or without nephritis, not included in previous groups.

TABLE 7.—*Mitral Stenosis (Pure)* *

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
905	−15	120	3	3
1917	−11	69	2	2
2300	−17	102	2	2
2275	−15	130	1.8	2
1905	−8.5	81	1.5	2.7
3895	−13	95	1	4
3252	−19.5	120	2.2	2.2
2362	2	50	1.5	3.5
6953	−1	59	2	3
6985	−30	90	1	3
6975	−4	62	2	3.5
6801	−7	75	1.5	3.5
6805	−6	90	2.2	1.8
6959	−10	72	1.5	3
6948	5.5	25	2	4
8518	−12	96	2	5
7151	−5	69	1	4
6471	−16	117	2	4
7106	−6	76	1	5
6898	−20	112	1.5	5
1324	−13	121	1.6	2.5
2983	−10	78	1.5	3.2
6556	−20	122	2	2.5
1355	−21	122	2.5	4
7859	−3	64	Auricular fibrillation	
9620	−14	126	Auricular fibrillation	
1396	−19	105	3	2.5
6763	−10	133	Auricular fibrillation	
6004	−8	90	Auricular fibrillation	
6765	0	—	1.5	2
6818	−9	140	1.5	1.2
6884	−17	98	Auricular fibrillation	
6890	−2	70	Auricular fibrillation	
6906	−20	112	Auricular fibrillation	
7109	4	−35	Auricular fibrillation	
7169	10	10	1	2
6411	−17	90	Auricular fibrillation	
6430	−20	97	Auricular fibrillation	
6440	−11	127	Auricular fibrillation	
6945	−30	90	1	1
5311	−19	88	Auricular fibrillation	
6879	−28	102	1.2	2.5
6450	−24	121	Auricular fibrillation	
5908	−14	80	Auricular fibrillation	
5822	5	52	Auricular fibrillation	
5003	4	0	Auricular fibrillation	
3883	−20	87	Auricular fibrillation	
5119	−10	90	Auricular fibrillation	
5007A	−15	97	Auricular fibrillation	
5275	−15	109	Auricular fibrillation	
4685	0	58	Auricular fibrillation	
5045	−8	108	Auricular fibrillation	
6863	−5	55	Auricular fibrillation	
5792	4	40	Auricular fibrillation	
5007	−18	110	Auricular fibrillation	
3640	−15	115	Auricular fibrillation	
5849	−10	158	Auricular fibrillation	
6031	8	−15	Auricular fibrillation	
4183	2	−32	Auricular fibrillation	
4531	−16	115	Auricular fibrillation	
4853	−2	60	Auricular fibrillation	
4063	−11	60	Auricular fibrillation	
4376	4	−11	1	2
4200	−8	76	Auricular fibrillation	
4529	−2	68	Auricular fibrillation	
3780	−12	115	Auricular fibrillation	
4717	12	7	Auricular fibrillation	
4685	2	55	Auricular fibrillation	
4710	5	−17	1	2
3608	16	5	1	2
3716	3	46	1	2
5562	−32	122	2	2.5
8518	−12	98	3	5
6435	−9	68	2.5	4
6064	−8	90	Auricular fibrillation	
7057	−11	99	2.5	5
6308	−3	67	2	3

TABLE 7.—*Mitral Stenosis (Pure)*—Continued*

Plate No.	Index, Mm.	Angle, Degrees	P_1, Mm.	P_2, Mm.
6325	−23	98	2	2.5
6535	−13	99	2	3
6831	15	−18	1.5	3+
6774	−44	164	2	2
6935	−9	108	2	2.5
7104	−13	92	2	2.5
5023	0	60	1.5	2
6233	−1	62	2	3
4476	2	42	2	3
4501	−9	73	2	2
6525	−10	90	3	3
2159	8	0	Auricular fibrillation	
4491	5	47	Auricular fibrillation	
8160	−5	74	Auricular fibrillation	
2450	−16	82	Auricular fibrillation	
3339	−18	142	2	2
3370	9	−16	1	1
2303	4	52	1.5	2.2
3182	−10	80	1.2	3
1742	−15	86	1.5	2.5
3319	1	57	1	1
3252	−20	120	2	2.5
3287	−6	69	1	1.5

* All were patients in the Massachusetts General Hospital electrocardiographed from 1918 to January, 1924.

Summary: Total cases, 100, including forty-two cases of auricular fibrillation. Of the remaining fifty-eight, forty-five had P_1 greater than 1 mm. amplitude (78 per cent.) and thirty-nine had P_2 greater than 2 mm. Twenty-six had P_2 equal to or greater than 3 mm. (45 per cent.); forty-nine had an abnormally large P_1 or P_2 (84 per cent.). Of the total (100) cases, forty-seven had angles equal to or greater than +90 degrees; seventy-four had angles equal to or greater than +60 degrees. Fifty-two had indexes equal to or below −10; thirty-one had indexes equal to or below −15. Of the fifty-eight cases with normal rhythm the indexes and angles were as follows: twenty-six had indexes equal to or below −10; sixteen had indexes equal to or below −15; forty-three had angles equal to or greater than 60 degrees, and twenty-seven had angles equal to or greater than 90 degrees.

2. Of all the nineteen patients with congenital pulmonic stenosis electrocardiographed at the Massachusetts General Hospital from 1914 to 1924 (nine and one-half years) 79 per cent. had an abnormally large P wave in Lead I, greater than 1 mm. in amplitude; 84 per cent. had an abnormally large P wave in Lead II, equal to or greater than 3 mm. in amplitude; 68 per cent. had both, and 100 per cent. had one or the other. Also, all showed abnormal right axis deviation (right ventricular preponderance).

3. Of the 100 unselected consecutive patients with mitral stenosis electrocardiographed at the Massachusetts General Hospital fifty-eight had normal rhythm. Forty-two showed auricular fibrillation. Of the fifty-eight cases with normal rhythm forty-nine (84 per cent.) showed either an abnormally large P_1, P_2 or both.

4. An amplitude of P_1 greater than 1 mm., of P_2 equal to or greater than 3 mm., an electrical axis of 90 degrees or more, and an axis index of — 10 or less are consistently found in congenital pulmonic stenosis.

5. A P_1 consistently greater in amplitude than 1 mm. or a P_2 equal to or greater than 3 mm. points to the possibility of an existent mitral stenosis; if both of these conditions are present there is greater likelihood of the condition; and if either of these findings is accompanied by right axis deviation, in the absence of pulmonic stenosis, the diagnosis of mitral stenosis is probable.

THE ACTION OF PARAPHENYLENDIAMIN

AN EXPERIMENTAL STUDY

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In the course of studies on the lymphatic system of the eye I made use of a drug that is known to produce edema of the orbital tissue and bulging of the eyeball. This drug is paraphenylendiamin hydrochlorid, which is used in dyeing furs and feathers and which also is the chief constituent of certain hair dyes. According to Birch-Hirschfeld,[1] the edema produced by this substance is essentially stasis of lymph, the result of which is dilatation of the lymph vessels, and he states that he has been able by this means to demonstrate a lymphatic apparatus in the orbital tissue. My observations of the action of paraphenylendiamin on the lymphatic system have been discussed in a previous paper.[2] Because of the peculiar symptom complex that follows the injection of paraphenylendiamin and because of very marked differences in the effect of the drug in different species of animals, I carried on the experiments on a much larger scale than my original purpose called for. Many of the symptoms arising from paraphenylendiamin poisoning bear a peculiar resemblance to those observed in poisoning from a group of substances collectively called "histamins." The question of a possible relationship of paraphenylendiamin to the histamin group was, however, not included in my experimental study of the former drug.

To those familiar with the symptoms of histamin poisoning their similarity to the symptoms of paraphenylendiamin poisoning in men engaged in dyeing furs and feathers and occasionally in people using the hair dye must indeed be striking. Kobert [3] states that in 30 per cent. of the men who are employed in dyeing skins the effect of the drug is not only manifested by eczematous eruptions and other affections of the skin, but that the respiratory tract also is involved, and that periodical attacks of asthma occur. These attacks resemble those of genuine so-called bronchial asthma even in the composition of the sputum in which Charcot-Leyden crystals, Curschmann's spirals and Ehrlich's eosinophil cells are found.[4] In view of these facts Erdmann,[5] the

1. Birch-Hirschfeld, A.: Die Krankheiten der Orbita, Graefe-Sämisch, Leipzig, **9**:112-114 (Part II) 1907.

2. Dewey, K. W.: A Study of the Lymphatic System of the Eye, Anat. Rec. **10**:125, 1925.

3. Kobert, P.: Lehrbuch der Intoxikationen, Stuttgart, 1906, **2**:653.

4. Griegern: Ueber eine gewerbliche Vergiftung beobachtet bei der Rauchwarenfärbung mit Paraphenylendiaminpräparaten, welche unter dem klinischen Bilde eines Bronchialasthmas verläuft, Verhandl. d. Cong. f. inn. Med. **20**:457, 1902.

5. Erdmann, E.: Ein neues Verfahren zum Färben von Pelzwerk, Ztschr. f. ang. Chemie **8**:424, 1895.

inventor of this dye for skins and feathers, was induced to make the express statement that the drug is not applicable for the dyeing of human hair. The symptoms that may arise after the use of the drug as a hair dye are eczema, lacrimation, reddening and swelling of the conjunctiva, chemosis, glaucoma and exophthalmos; also such general symptoms as vomiting and diarrhea may be observed. In a case described by Puppe,[6] skin eruptions appeared on the scalp and the neck the same day the woman applied the hair dye; the next day the face was so swollen that she could not open the eyes. All symptoms disappeared within a short time. Puppe was told by the patient that similar symptoms had occurred in other women who had used the dye. Pollack [7] reported a case in which the symptoms appeared after the third application; several months had elapsed since the first and second applications. The symptoms were itching, burning and eczematous swelling of the skin, lacrimation, swelling of the lids and exophthalmos.

In animals the effects vary considerably with the species. It may be said that there is a marked idiosyncrasy for the drug. The observations with the hair dyes emphasize this; many people apparently have no symptoms from it while some react more or less violently.

Paraphenylendiamin is considered as being on the borderline of the blood poisons. If it is mixed with blood, brown discoloration and the formation of methemoglobin is observed. In the body brown discoloration also takes place, but methemoglobin is not formed, or is formed only to a slight degree. There is no explanation yet for the action of paraphenylendiamin and the peculiar changes about the eye. Puppe and also Kunkel [8] are of the opinion that the blood and the blood vessels are essentially involved in the development of the intoxication edema which is the most characteristic feature of paraphenylendiamin poisoning. Tainter and Hanzlik,[9] in testing the drug in rabbits, found that while specific edema of the head and neck develop in from one to three hours after subcutaneous injection of the drug (0.19 gm. per kilogram) there is at the same time a relative increase in the hemoglobin and the total solids of the blood due to the escape of fluid from the circulation; this indicates that an increase in vascular permeability may be a factor in the production of the edema.

The features observed in paraphenylendiamin poisoning described in the foregoing vividly recall the peculiar symptoms characteristic of

6. Puppe: Ueber Paraphenylendiamin Vergiftung, Vritljschr. f. gerichtl. Med. **12**:1161 (Supp.) 1896, p. 1161, quoted by Matsumoto (Footnote 13).

7. Pollack, E.: Ein Fall von Paraphenylendiaminvergiftung, Wein. klin. Wchnschr. **13**:712, 1900.

8. Kunkel, A. J.: Handbuch der Toxikologie, Jena, 1901, p. 616.

9. Tainter, M. K., and Hanzlik, P. J.: The Mechanism of Edema Production by Paraphenylendiamin, Proc. Soc. Exper. Biol. & Med. **20**:497, 1923.

histamin poisoning. It would seem that these two substances are too widely different for a common action; yet we know today that a variety of substances that apparently are entirely unrelated in their chemical make-up have the typical histamin action. First of all, it was found that the substances termed "histamin," "peristaltic hormone," "vasodilatin" and "motlin" are all the same substance. It was shown that other substances, like pituitary extract, although from other tissue organs also have the typical histamin action; that in fact this action is common to a large group of poisonous substances of animal and vegetable origin. With reference to the edema from histamin poisoning the view is expressed that it is due to the action of histamin as a poison to the capillary endothelium. "This again," Abel and Kubota[10] state, "brings them into relation with certain metallic poisons, such as arsenic and gold salts which were long ago classed by Huebner as 'capillary poisons,' and which when introduced in appropriate doses into the general circulation, produce a shocklike prostration." They remark further on:

> The existence of these points of community, in the action of substances so utterly unrelated chemically as histamin and certain metallic ions, forbids any assumption that the production of similar effects by unknown constituents of some organ or tissue indicates the presence therein of histamin itself, or of any substance chemically related to it.

The dog is the animal most susceptible to the toxic action of paraphenylendiamin introduced subcutaneously. The lethal dose is 0.1 gm. per kilogram of body weight, with death occurring from two to three hours after the injection. Half this dose is sufficient to produce marked symptoms. In the rabbit very much larger doses are required and the injections may be repeated; but ultimately the same effect will be obtained. Intravenous injections, according to Pollack, do not produce these characteristic symptoms. However, he tested this only once. My own repeated experiments showed that his statement is not correct, and Kobert and Dubois and Vignon[11] also state that they obtained edema of the subcutaneous tissue, and especially about the eye, by introducing the drug directly into the circulation. The peculiar eye symptoms may also be produced by scarification of the skin, as in fact the effects of the hair dye on the skin would lead us to suppose.

The symptoms of paraphenylendiamin poisoning that we observe in dogs have been described by Grunert as follows: The earliest and most

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10. Abel, J., and Kubota, S.: On the Presence of Histamin (β-Iminazolylethylamin) in the Hypophysis Cerebri and Other Tissues of the Body and Its Occurrence Among the Hydrolytic Decomposition Products of Proteins, J. Pharm. & Exper. Therap. **13**:243 (June) 1919.

11. Dubois and Vignon: Action physiologique de para et métaphénylènediamine, Compt. rend. Soc. de biol. **107**:533, 1888.

striking symptoms are chemosis and exophthalmos with an increase of the intra-ocular pressure. This is accompanied by increased lacrimal and mucous secretion of the conjunctivae and an increase of the saliva. With a large dose the edema of the orbit passes over to the face and to the neck. There is vomiting, diarrhea, paralysis, trembling, apathy, and under dyspnea and convulsions death occurs in coma within from three to six hours after the injection. Anatomically, the poisoned animals show serous effusion of the orbital cellular tissue, black discoloration of the lacrimal glands, slight brown discoloration of the tongue and gingivae, swelling of the entire mucosa of the upper air passages, and above all edema of the tongue and glottis. The other findings in the inner organs are in general negative. Edema of the glottis is to be considered as the cause of death. Besides the lacrimal gland, the gland of the nictitating membrane is discolored; some portions of the orbital gland also are sometimes slightly browned; both submaxillary glands are always, although slightly, discolored. On the other hand, the parotid, the thyroid and the thymus glands, the lung, liver, pancreas, testes and Peyer's plaques are always normal.

Grunert [12] does not explain where the fluid in the edematous tissue comes from. It is a fact that the edema fills the entire orbit as early as one hour after the injection and disappears again in one day without leaving any demonstrable traces. No cellular infiltration is ever found about the glands as an indication of an irritation. Grunert states that the edematous fluid pressed out of the tissue does not differ in reaction nor in its other chemical behavior from normal lymph, but is well distinguished from inflammatory edema. He believes, therefore, that we must assume that the substance is made ineffective or is bound in the lacrimal gland. Not so in the salivary glands, which excrete the poison unsplit. The orbital edema is therefore, he states, congestion or stasis of normal lymph, which, according to Matsumoto, is apparently in the state of coagulation, for it does not flow off when the edematous tissue is cut into. Puppe believes that it is a stasis edema, perhaps due to the formation of thrombi in the veins.

Matsumoto and Kunkel are of the opinion that the substance circulating in the blood passes from the peripheral capillaries into the lymph and there produces certain chemical changes of the lymph impeding its forward motion. An analogy in the action of this poison is offered by potassium iodid, which also produces coryza and edema of the glottis. Grunert asserts that he has shown that the lacrimal gland by a special property of the protoplasm of its secreting cells is able to render this poison chemically ineffective. Tainter and Hanzlik found that localiza-

12. Grunert, K.: Die Augensymptome bei Vergiftung mit Paraphenylendiamin nebst Bemerkungen über die Histologie der Tränendrüse, Ber. ü. d. Versamm. d. ophth. Gesellsch., 1903, pp. 31-32, 208.

tion of the edema in the head and neck of the rabbit is not connected with an increased concentration of paraphenylendiamin in these regions, since quantitative estimations of the paraphenylendiamin in the saliva and in the edematous fluid showed the concentration to be less or no greater than that in the blood plasma. They also state that oxidation products are not concerned in the edema.

Matsumoto [13] tested the drug on frogs and mice as well as on dogs and rabbits. If frogs are brushed with a 15 per cent. solution of paraphenylendiamin on different parts of the body, torpor, paresis and gradually complete paralysis are observed. At the necropsy the superficial muscles are markedly blue; this coloration increases in contact with the air. Matsumoto believes that the oxygen of the air diffuses through the skin to the muscles and that oxidation does not take place through the oxygen circulating in the blood. Subcutaneous injection of 0.01-0.02 gm. of paraphenylendiamin kills frogs weighing 40-60 gm. Paresis and paralysis are the chief symptoms. The subcutaneous cellular tissue contains large quantities of clear fluid. There is pigmentation of the liver and spleen and bluish red coloration of the superficial muscles. Mice are killed by as little as 0.005 gm. of paraphenylendiamin. Paresis is soon observed and death occurs under convulsions within one hour. There is no edema of the subcutaneous tissue nor pigmentation of the liver and spleen worth mentioning. The muscles turn brownish red. Rabbits may be killed by intravenous injection of 0.2 gm. of paraphenylendiamin per kilogram of body weight. The symptoms are salivation, edema of the tongue, trismus, subcutaneous edema of the lower portion of the face and the upper portion of the neck, paresis, convulsions, dyspnea, and even suffocation followed by death. The eye symptoms are not prominent; however, exophthalmos, chemosis and edema of the lids are sometimes observed. In dogs he observed the same symptoms as other authors. To him the most plausible explanation for the phenomenon seemed that the paraphenylendiamin circulating in the blood is in part eliminated into the lymph from the peripheral capillaries. About the head the poison meets the proper conditions for certain chemical alterations which lead to coagulation or at least impeded flow of the lymph. The edema in these conditions differs from that in man, Matsumoto believes; when cutting into such tissue, this appears gelatinous, while in edema in man clear fluid flows out.

A summary of my experiments will show that, in general, the symptoms I observed are the same as those reported by the writers

13. Matsumoto, H.: Ueber die Giftwirkung des Paraphenylendiamins, I. D., Würzburg, 1901.

I have mentioned, but that there are some observations which have not been reported or duly emphasized by these writers.

The most characteristic effect of paraphenylendiamin, namely, edema of the orbital tissue with exophthalmos and lacrimation, is observed best in the dog. This animal is the most susceptible to the action of the drug. The lethal dose is 0.1 gm. subcutaneously, with death occurring from two to three hours after the injection. Rabbits can stand very much larger doses than dogs. The dose of 0.1 gm. per kilogram, fatal to dogs, has to be given several times to rabbits before the characteristic symptoms arise. A single dose of 0.5 gm. will produce death within from two to three hours. Edema of the glottis is the immediate cause of death. Exophthalmos is rarely observed in rabbits. Edema of the subcutaneous tissue of the face and neck, of the glottis and the upper air passages is the most conspicuous symptom. In frogs the characteristic symptoms are of a nervous nature: torpor, paresis and paralysis. In guinea-pigs they are exclusively nervous: excitement and convulsions. There is no swelling of the subcutaneous tissue. The symptoms in dogs are restlessness very soon after the injection, vomiting, purging, swelling of the conjunctivae and the lids, well noticeable one and one-half hours after the injection; sensitiveness of the eyes to light, uneasiness, groaning, respiratory disturbances, and a comatose condition after three and one-half hours when the dose is less than 0.1 gm. per kilogram. Cats react very similarly to the drug. Constriction of the pupil, respiratory disturbances and edema of the glottis are conspicuous symptoms.

Since the statements about the effects of paraphenylendiamin in rabbits vary somewhat and apparently the experiments with them by other writers have not been extensive, I give a table of my observations on rabbits. A table of the effect on guinea-pigs is added; evidently no tests on those animals have yet been made.

When we consider these symptoms, the action of paraphenylendiamin seems to differ widely in animals. The strictly localized edema, the most conspicuous symptom in dogs, cats and rabbits, seems to have nothing in common with the nervous manifestations, the main symptom observed in guinea-pigs, frogs and mice in which edema does not occur. The peculiar localization of the edema is such a striking feature in the former group of animals that it has received the chief attention from all investigators. No satisfactory explanation of this singular action of paraphenylendiamin has yet been offered. Some writers have attempted to explain the steps in which the edema may be produced; it has not been suggested that primarily the cause may be from the nervous system. Nervous manifestations, however, are actually observed in dogs and cats very early; they are even the very first symptoms. Soon

TABLE 1—*Effect of Paraphenylendiamin on Rabbits*

Rabbit No.	Weight, Gm.	No. of Injections	Dose per Kg. of Body Weight, Gm.	Kind of Injection	Interval Between Injections	Interval Between First Injection and Death	Time of Onset of Symptoms	Symptoms	Cause of Death	Remarks
1	1,080	3	0.1	Subcutaneous	24 hours	4 days	From 5 to 6 hours after first and second injections; 2 hours after third injection; death 12 hours later	Edema on face and neck, salivation, torpor; swelling always very much reduced after 24 hours	Not edema of the glottis; intoxication?	Apparently this rabbit was more susceptible to the drug than most rabbits
2	1,580	5	0.1	Subcutaneous	24 hours between third and fourth injections; 48 hours between fourth and fifth injections	5 days	No symptoms after the first and second injections; swelling, torpor, anorexia 2 hours after third injection; no edema after fourth and fifth injections; death 2 hours after fifth injection	Edema, salivation, torpor, anorexia; edema following the third injection disappeared and did not arise after the fourth and fifth injections; torpor and anorexia remained	Not edema of the glottis; intoxication?	
3	800	2	0.15	First, intravenous; second and third, subcutaneous	19 hours between first and second injections; 2 hours between second and third injections	23 hours	No symptoms after the first and second injections; they arose after third injection	Edema on face and neck, salivation, dyspnea after the third injection; death 2 hours after the third injection	Edema of the glottis	
4	1,645	3	0.15	First and second subcutaneous; third intravenous	4½ hours between first and second injections; 20 hours between second and third injections	25 hours	No symptoms after the first injection; they arose late after the second; death ½ hour after third injection	Slight edema, torpor and anorexia after the second injection; death ½ hour after the third injection	Edema of the glottis	Violent local reaction; sloughing of epidermis at place of injection
5	510	1	0.3	Subcutaneous	.....	12 hours	Several hours after the injection	Marked edema of the face; salivation; dyspnea	Edema of the glottis	
6	1,070	2	0.35	Subcutaneous	18 hours	20 hours	No symptoms after the first injection; death 2 hours after second injection	Salivation; dyspnea; edema over lower portion of neck	Edema of the glottis	Brown discoloration of muscles; no edema about eyes
7	985	1	0.3	Intravenous	.....	16 hours	Symptoms several hours after injection	Enormous swelling of subcutaneous tissue over upper portion of neck	Killed before it had time to die from edema of the glottis	
8	780	1	0.5	Subcutaneous	.....	2 hours	1¼ hours after the injection	Dyspnea from edema of the throat and tongue	Edema of the glottis	No edema about the eyes
9	1,400	4	0.1	Intravenous	3 days	13 days (killed)	.....	No symptoms	.....	Lockjaw but not from drug; several normal rabbits had it
10	1,270	5	0.1	Subcutaneous	3 to 4 days	21 days	.....	No symptoms	.....	Marked sloughing of skin at place of injection

TABLE 2.—*Effect of Paraphenylendiamin on Guinea-Pigs*

Guinea-Pig Number	Weight, Gm.	Number of Injections	Dose per Kg. of Body Weight, Gm.	Kind of Injection	Interval Between Injections	Interval Between Injection and Death	Time of Onset of Symptoms	Symptoms	Remarks
1	280	4	0.125	Subcutaneous	4 days	13 days	Early after fourth injection; death 50 minutes after the third injection	Excitability	
2	280	3	0.125 0.250	Subcutaneous	4 days	9 days	Early after third injection; death 2 hours after the third injection	Convulsions	Sores at place of injections
3	480	2	0.140	Intraperitoneal	3 days	3 days	Symptoms arise slowly after the second injection; death over night	Twitching in hind legs; excitability; final symptoms could not be observed	
4	380	2	0.200	Intraperitoneal	3 days	3 days	One hour after second injection; death over night	Twitching in hind legs; excitability; final symptoms could not be observed	
5	600	2	0.058 0.150	Subcutaneous	3 days	3 days	Slight nervous manifestations after first injection; violent symptoms arose almost at once after second injection; death 35 minutes after injection	Convulsions until death	Guinea-pigs 5 and 6 had been treated like frogs for 24 days by daily repeated external applications of the drug; no symptoms occurred; the animals gained in weight, but apparently there was some absorption
6	400	2	0.062 0.200	Subcutaneous	3 days	3 days	Slight nervous manifestations after first injection; violent symptoms ½ hour after the second injection; death 4 hours after injection	Animal constantly moves in a circle from right to left	

after the injection the animal becomes restless; there are disturbances in the locomotion; the head is thrown back, as in opisthotonos, before there are manifest indications of respiratory interference from bronchial spasm or edema in the air passages. Dubois and Vignon [11] also report such symptoms. It would not seem unreasonable to assume that the edema occurring in man and dogs is due to paralysis or irritation of the vasomotor nerves, resulting in an increase of the vascular secretion.

It is of interest to note that the manifestations of the toxic action of paraphenylendiamin in men employed in dyeing skins are of a type that may be classed with the so-called neuropathic affections; namely, certain skin eruptions which, like urticaria, herpes zoster, etc., are probably intoxication symptoms associated with nervous disturbances in the functions of the capillaries. Moreover, the bronchial asthma that attacks a rather high percentage of the men who are exposed to the action of paraphenylendiamin in their occupation is a "neurosis." The action of this drug may be in all cases on the nervous system, and nervous influences exerted on the capillaries may be the direct cause of the edema. The localization is a peculiar feature. The edematous swelling of the orbital tissue in dogs is very striking; but the edema in the upper air passages leading to death from suffocation is not less remarkable. In rabbits the edema of the subcutaneous tissue of the face and the neck, of the tongue and the throat is much more marked than about the eyes.

Why the action of a toxic substance on the nervous system should evoke a localized edema is not at once clear. We may assume that nervous influences may be exerted directly on the capillaries and that in the region of the eyes, in the throat, the face and the neck the capillaries may have certain properties peculiar to them and adjusted to functional activities in these regions, and that it is because of these properties that edema is produced by neuropathic influences in these regions only and not in others. This inference is possible in view of the fact that the transudates differ one from another in various localities. I refer here only to statements by Ziegler [14] that the albumin content of pure transudates is not the same in all body cavities and tissues, but differs in a pronounced degree. The albumin content of transudations of the pleura, according to Reuss, is 22.5 per thousand; that of the pericardium 18.3; of the peritoneum 11.1; of the subcutaneous connective tissue 5.8; of the cavities of the brain and spinal cord 1.4. To these statements Ziegler adds the remark: "These facts may be taken as a proof of the different constitution of the vessel walls in the various tissues of the body."

14. Ziegler, E.: General Pathology, translation, New York, 1918, p. 153.

For comparison let us recall some observations of the action of histamin in animals. Dale and Laidlow [15] observed immediate vomiting and purging, profuse salivation and labored respiration followed by a period of collapse in a cat injected intravenously with 10 mg. of the hydrochlorid of histamin. There is a marked idiosyncrasy in the species of animals, especially in rodents. In the latter, the effects of intravenous and subcutaneous injections are conspicuous features in histamin poisoning. Death is due to asphyxia from constriction of the bronchioles by spasm of the muscular coats, perhaps also from increased secretion. With smaller doses there is recovery of the symptoms; a second injection before the effects of the first have entirely subsided causes renewal of the symptoms in an accentuated form, death ensuing in a few seconds. Large doses produce convulsive and obstructed respiration. In cats there is not such a marked discrepancy between the effects of intravenous and subcutaneous injections. Salivation, lacrimation and increased bronchial secretion are observed. Constriction of the pupil, even in the dusk, is a notable feature.

Concerning the bronchial spasm, Dale and Laidlow remark that it is impossible to say whether histamin has a direct effect on the respiratory center. Barger and Dale [16] state that histamin increases the flow of lymph from the thoracic duct. Interesting are the views of Keeton, Koch and Luckhardt [17] concerning the observations made by Dale and Richards [18]:

> Their observations indicate a remarkable vascular action by histamin. Apparently it acts upon two distinctly different anatomical structures in the vascular system. It causes a transient vasoconstriction in the arterioles and a more delayed and prolonged vasodilating action on the capillaries due to inhibition of their tone. The main action then consists in opening up new capillary areas together with permeation of the capillary wall by blood plasma—Dale and Richards' observations indicating a loss of plasma and an increase in concentration of red corpuscles in the blood, as a result of histamin, have also been observed by Simon.[19]

The striking dissimilarity in the action of paraphenylendiamin in different animals has an interesting analogy in one of the most charac-

15. Dale, H., and Laidlow, P.: The Physiological Action of β-Iminazolylethylamine, J. Physiol. **41**:318, 1910; Further Observations on the Action of β-Iminazolylethylamine, J. Physiol. **43**:183, 1911-1912.

16 Barger, G., and Dale, H.: β-Iminazolylethylamine, a Depressor Constituent of Intestinal Mucosa, J. Physiol. **41**:499, 1911-1912.

17. Keeton, R. W.; Koch, F. C., and Luckhardt, A. B.: Gastrin Studies, III, The Response of the Stomach of Various Animals to Gastrin Bodies, Am. J. Physiol. **51**:454 (April) 1920; IV, The Response of the Stomach Mucosa to Food and Gastrin Bodies as Influenced by Atropin, ibid. **51**:469 (April) 1920.

18. Dale, H. H., and Richards, A. N.: The Vasodilator Action of Histamin and of Some Other Substances, J. Physiol. **52**:110 (July) 1918.

19. Simon, L. G.: Sur Quelques Effects des Injections de Sécrétine, J. de physiol. et de path. gén. **9**:79, 1907.

teristic actions of epinephrin or pituitary extract (histamin), namely, that on the plain muscle of the uterus. Keeton, Koch and Luckhardt, in reference to this, state:

> It is well known that the virgin or nonpregnant uterus of the rabbit, dog, ferret, monkey or man always contracts after adrenalin treatment whereas in the cat, guinea-pig and rat this may cause a relaxation, and that only the pregnant uterus is caused to contract.

SUMMARY

1. There is a marked difference in the susceptibility to paraphenylendiamin not only in species of animals but also in individuals of the same species.

2. In people with an idiosyncrasy for the drugs paraphenylendiamin (in an industrial occupation or after the use of the hair dye) produces local and general symptoms that resemble somewhat those observed in the dog. The drug apparently is absorbed by the skin to some extent.

3. Some animals (individuals, not species) show a more or less violent local reaction, resulting in sharp demarcation of an area with ultimate sloughing.

4. Dogs are the most susceptible to the drug. A fatal dose is 0.1 gm. per kilogram of body weight with death occurring from two to three hours after the injection. Marked symptoms are produced by 0.05 gm. Cats react similarly.

5. Doses fatal to dogs may be given from three to five times to rabbits without producing any symptoms if the intervals (from three to four days) are long enough to permit elimination of the poison. With short intervals (from four to twenty-four hours) symptoms generally arise after the third injection. A dose of 0.34 gm. injected subcutaneously or intravenously produces death within twelve hours.

6. Guinea-pigs, like rabbits, are not affected by a subcutaneous dose that is fatal to the dog. Symptoms arise after the third or fourth injection of 0.125 gm., if the intervals are four days. Intraperitoneal injections act more quickly. If paraphenylendiamin is applied externally for some time, a small dose injected subcutaneously is sufficient to produce symptoms.

7. Frogs are very susceptible to the poison applied externally; it is rapidly absorbed by the skin. Death may occur one hour after the application.

8. The symptoms in dogs, cats and rabbits are a localized edema. In guinea-pigs, mice and frogs they are nervous manifestations: paresis, paralysis or convulsions.

9. The action of the drug is perhaps in all cases on the nervous system. The edema about the head may be the result of vasodisturbances. The localization may correspond to differences in the constitution of the vessel walls in the involved areas.

INTERMITTENT AURICULAR FIBRILLATION

WITH FLEETING RAPIDLY RECURRING PAROXYSMS HAVING IDENTICAL TYPE OF AURICULAR BEHAVIOR *

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It has become recognized during the last few years that paroxysmal auricular fibrillation is a relatively common disorder, although probably not so frequent as chronic fibrillation. According to the published descriptions of cases, it would appear that the paroxysms usually last hours or days; nevertheless, all clinicians of experience must occasionally have encountered paroxysms lasting only a few minutes, particularly in cases of hyperthyroidism but also occasionally in other forms of cardiac involvement.

Very brief paroxysms, not more than a few seconds in duration, have been very rarely observed. This may be due in part to the impossibility of recognizing the nature of such brief paroxysms by ordinary clinical methods and to the fact that unless they recur frequently they are recorded in electrocardiograms by mere chance. A careful search of the literature extending over the period of use of the electrocardiograph in clinical medicine for examples of such fleeting paroxysms reveals only four cases reported with electrocardiograms that leave no doubt as to the correctness of the interpretation. Possibly other cases not readily accessible have been overlooked.

Semerau,[1] in 1918, reported two cases in which fleeting paroxysms were recorded. In one of these, however, the paroxysms did not occur spontaneously but could be elicited by exertion or excitement. Smith and Moody,[2] in studying a patient who gave a history of paroxysmal cardiac attacks, were able to evoke short paroxysms of fibrillation during the expiratory phases of forced breathing. Recently, Wedd [3] has reported a case in which coarse wave fibrillation was present when the patient entered the hospital, but on the following day many paroxysms of auricular fibrillation, some of which were extremely fleeting, occurred.

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1. Semerau, M.: Ueber Rückbildung der Arhythmia Perpetua, Deutsch. Arch. f. klin. Med. **126**:161 (May 24) 1918.

2. Smith, F. M., and Moody, W. B.: The Induction of Premature Contractions and Auricular Fibrillation by Forced Breathing, Arch. Int. Med. **32**:192 (Aug.) 1923.

3. Wedd, A. M.: Clinical Auricular Flutter, Ann. Clin. Med. **3**:69 (July) 1924.

In Wedd's patient, following the use of quinidin several fleeting paroxysms of auricular flutter also were recorded.

A case we have recently studied is of interest on account of the remarkable brevity, general similarity to each other and rapid recurrence of paroxysms. A number were recorded sufficient to afford an opportunity of making observations on the mode of onset of fibrillation, comparisons of the course of the excitatory process in various paroxysms, the mode of offset and the duration of "postundulatory" pauses.

The extreme brevity and rapid recurrence of paroxysms in the case to be reported, resembling the behavior of intermittent auricular flutter, which I have recently described,[4] and intermittent paroxysmal auricular tachycardia, described by Kure and Sakai[5] and others, has suggested that the name intermittent auricular fibrillation be reserved for this condition. The name has been used by some writers, rather unhappily, to apply to the ordinary clinical forms of paroxysmal auricular fibrillation.

The patient was referred for electrocardiographic study by Dr. Hobart A. Hare, to whom I am indebted for the privilege of reporting the case.

REPORT OF CASE

T. S., a robust, healthy looking man, aged 56, had been seen by Dr. Hare from time to time during a number of years because of hypertension. No arrhythmia had been noted by Dr. Hare prior to June 11, 1924, when marked irregularity of the cardiac action was found. The examination was otherwise essentially negative except for marked diminution of the pulse in the right brachial, radial and carotid arteries. It was suspected that this was caused by some lesion of the aorta or innominate artery, possibly aneurysm, although no direct evidence of aneurysm could be obtained either clinically or by roentgen ray. There was no evidence of syphilis.

The electrocardiograms of June 11 are shown in Figures 1 and 2. Frequent premature auricular beats which occur irregularly are found. Some of the premature beats are isolated but others are followed by fibrillary after-effects of varying lengths, represented in the tracings by one up to ten irregular auricular oscillations and lasting from a fraction of a second to over two seconds. The majority of the after-effects are represented by four or five waves and have a duration of about one and one-half seconds. Their intermittent distribution and rapid recurrence are shown in the tracings. According to Dr. Hare's observation, this special form of arrhythmia must have lasted for a number of days. The lack of regularity in shape and time relations of the oscillations indicates that these disturbances of rhythm must be due to auricular fibrillation as they are far too irregular to be regarded as forms of so-called "impure" flutter.

The patient was sent back for another tracing June 21, and at this time there was found continuous fibrillation. Several tracings have been made since that

4. Wolferth, C. C.: Intermittent (Impure) Auricular Flutter, with Special Reference to Onsets and Offsets of Paroxysms and the Effects of Vagus Stimulation, Arch. Int. Med. **35**:42 (Jan.) 1925.

5. Kure, K., and Sakai, S.: Ein Fall von intermittierend Auftreten der heterotoper Vorhofstachysystolie, Deutsch. Arch. f. klin. Med. **140**:67 (July 25) 1922.

time, the last on Dec. 4, 1924, all of which have shown continuous fibrillation. Cardiac compensation has been fairly well maintained in spite of several anginal attacks and the patient has carried on his usual work as a lawyer.

The continued repetition of fleeting paroxysms of auricular fibrillation observed during the first examination must be attributed to a peculiar functional state of the auricular muscle. The celerity with which the disturbances followed one another indicates that the muscle was in an advanced stage of what Garrey [6] has called the "fibrillary state." Equally important for the production of such a form of arrhythmia was the fact that none of the disturbances were able to perpetuate themselves. Some time in the ten days intervening between

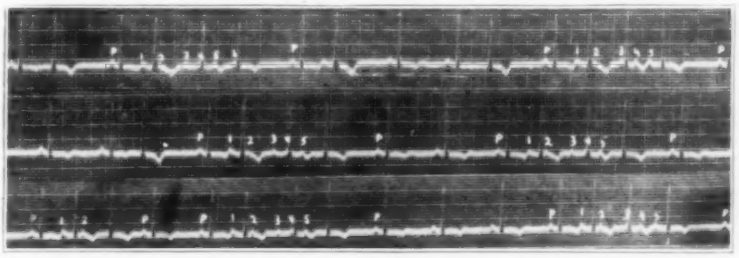

Fig. 1.—Several isolated premature auricular beats in Lead II; characteristic alternation of sinus rhythm and short paroxysms of auricular fibrillation; similarity of auricular portions of curves; a brief paroxysm in the left hand corner of bottom strip. Only those paroxysms ending alike (after the fifth auricular oscillation) have postundulatory pauses of similar length.

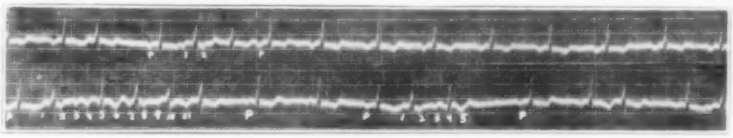

Fig. 2.—Isolated premature auricular beats in Lead III; one extremely brief paroxysm, one of intermediate length, and the longest one recorded.

the first and the second examination, a change must have occurred in the properties of the auricular muscle whereby it became possible finally for a paroxysm to be extended indefinitely into continuous or chronic fibrillation.

The course of events observed in this patient emphasizes sharply the fact that such alterations in functional properties of cardiac muscle, which make easy the spontaneous entrance of auricular fibrillation, are not exactly identical with the conditions that permit of the continuance

6. Garrey, W. E.: Auricular Fibrillation, Physiological Rev. **4**:215 (April) 1924.

of fibrillation. Normal heart muscle, if we may judge from experimental evidence, does not permit auricular fibrillation to perpetuate itself long, although there are wide individual variations in the lengths of paroxysms. When heart muscle is altered to the fibrillary state, the form of arrhythmia (paroxysmal or chronic) will depend on either preservation or loss of ability to terminate fibrillation spontaneously. Clinical observation appears to indicate that in many cases the first onset of fibrillation continues as chronic fibrillation. In such cases what might be called the functional capacity of terminating fibrillation is lost coincidently with, or possibly even before, the development of the fibrillary state.

Whether or not in our case the remarkable brevity of paroxysms in spite of the highly fibrillary state indicated temporary preservation of a normal type of reaction or was due to some accidental disarrangement in the mechanism that ordinarily maintains fibrillation in certain damaged hearts, the data do not permit us to say. In two cases of intermittent auricular flutter, I was able to present evidence in explanation of the brevity of paroxysms.[4] Although the mechanism differed somewhat in the two cases, the termination of flutter in both was due to failure of the excitatory process to elect a path in which equilibrium could be established between the rate of propagation of the impulse and the duration of the refractory phase. Possibly an analogous explanation might account for the brevity of paroxysms in our present case, but the curves in fibrillation are so irregular as to make analysis impossible.

MODE OF ONSET

Garrey[6] states that auricular fibrillation may arise from a normal impulse from the sinus region or any other impulse, no matter where it originates. In the clinical instances previously reported, nearly all onsets recorded were initiated through premature auricular beats. I have recently called attention to a similar rôle of premature auricular beats in exciting paroxysms of auricular flutter.[4] That clinical fibrillation may take its origin directly from a sinus beat has been shown clearly in a tracing published by Semerau.[1] In Semerau's case, fibrillation had been momentarily interrupted by vagus stimulation, and on its resumption was initiated by a sinus beat.

In our case premature auricular beats were concerned in the onsets of all paroxysms recorded. Except for the after-effect of fibrillation, they appeared identical in all respects with the numerous isolated premature beats. They all bore a close enough relationship to preceding beats to suggest coupling, but the lengths of the periods varied from 0.4 to 0.46 second. Whether these extrasystoles be regarded as the direct exciting cause of the fibrillation or as an intermediate bridge from the

preceding sinus beat depends on one's attitude toward the unproved view that extrasystoles are circus contractions. The point of practical importance is that auricular extrasystoles may and usually do play a highly conspicuous rôle in the initiation of auricular fibrillation, provided the fibrillary state is present.

PATH OF THE EXCITATORY PROCESS

Examination of the auricular portion of the curve in any of the paroxysms recorded appears to indicate an irregular, haphazard course of the auricular excitatory process, manifested by markedly irregular spacing and lack of uniformity in shape of the waves. Such a curve cannot be interpreted otherwise than as auricular fibrillation. Nevertheless, if all the paroxysms recorded in Figure 1 are compared, it is found that there is a remarkable similarity among them. They show significant variation in lengths of paroxysms only. So far as each one continues, the apparently irregular auricular curves can be practically superimposed on one another. Measurements of intervals between summits of waves vary by only slight differences. For example, in Figure 1, Strips 1 and 2, measurements of successive intervals between the first six summits, beginning with the normal P waves, are: 0.41, 0.26, 0.37, 0.18, 0.22 (total 1.44) seconds; 0.42, 0.26, 0.36, 0.20, 0.21 (total 1.45) seconds; 0.42, 0.26, 0.36, 0.19, 0.22 (total 1.45) seconds, and 0.43, 0.25, 0.36, 0.18, 0.22 (total 1.44) seconds, respectively. A similar relationship is also found among all the paroxysms recorded in Leads I and III. We are therefore justified in assuming that in spite of the apparent irregularity of the excitatory process, it does not wander haphazard but proceeds in a definite manner over a somewhat devious but identical course so far at least as these brief paroxysms can be compared.

Identity of auricular behavior among paroxysms of auricular fibrillation has not been demonstrated previously. Lewis, Drury and Iliescu,[7] in discussing clinical fibrillation, have called attention, however, to the fact that there appears to be a definite channel for which the central excitation wave shows a predilection; that sometimes it is forced out of this channel, but that, if this happens, the wave soon returns to its old path, repeating its old course and in the original direction. Lewis has repeatedly championed the view that in clinical fibrillation there is a single central excitation wave circulating in the auricular muscle. Such precisely circumscribed movements as occurred in our case could scarcely be explained without assuming the presence of a single central excitation wave.

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7. Lewis, T.; Drury, A. N., and Iliescu, C. C.: A Demonstration of Circus Movement in Clinical Fibrillation of the Auricles, Heart **8**:379 (Aug.) 1921.

OFFSETS OF FIBRILLATION AND "POSTUNDULATORY" PAUSES

The offsets, as in other recorded offsets of auricular fibrillation, are abrupt. Each was followed by a postundulatory pause. This name was apparently coined by Gewin [8] to designate the pause after cessation of experimental fibrillation before resumption of normal sinus beating. Such pauses had been noted following delirium cordis by Hoffa and Ludwig [9] as early as 1850. Winterberg [10] regarded them as analogous to the pauses after auricular extrasystoles. Semerau [1] mentions their occurrence in his cases of clinical fibrillation.

Garrey [6] has recently stated that a fibrillary beat may be initiated from the normal pacemaker and the impulse shuttle back and forth through auricular muscle producing rapid oscillations which may stop before the next impulse arises so that the normal rhythm is not disturbed in the least and there is no postundulatory pause.

In the condition mentioned by Garrey, the fibrillary wave presumably does not return to the sinus node. In longer paroxysms of auricular fibrillation, the centrifugal wave doubtless reaches the pacemaker as well as all other parts of the auricles so that, following the last stimulation of the pacemaker in this manner, time approximate to that of a normal cycle is required to build up and discharge an impulse. In Figure 1 the time of a normal cycle is approximately 0.82 second, and measurements from summits of isolated premature beats to summits of the next normal P waves vary from 0.99 to 1.01 seconds, indicating the presence of postextrasystolic pauses. Unfortunately, the curves do not permit of accurate measurements of postundulatory pauses, because ending of fibrillation is not sharply enough defined, but in the three paroxysms in Lead I that end similarly measurements from the summits of the last fibrillary waves to the summits of the following P waves are 1, 1.03 and 1.01 seconds, respectively; these correspond closely in time with the postextrasystolic pauses. All other postundulatory pauses are apparently shorter, varying from 0.79 to 0.88 second. It is of interest that even the most abortive manifestations of fibrillation, having a duration only a fraction of the length of a normal cycle, are followed by postundulatory pauses (Fig. 2).

Our measurements appear to indicate a wide variability in duration of the postundulatory pause. The variation may be more apparent than

8. Gewin, J.: Das Flimmern des Herzens, Arch. f. Anat. u. Physiol. (Physiol. Section) **247**, 1906.

9. Hoffa and Ludwig, quoted from Winterberg, H.: Studien über Herzflimmern, III, Mitteilung über das Wesen der postundulatorische Pause, Arch. f. d. ges. Physiol. **128**:471 (July 10) 1909.

10. Winterberg (Footnote 9).

real. Had we been able to determine the exact time of the last stimulation of the pacemaker during each paroxysm and measured from that point to the succeeding P wave, possibly a more constant relationship would have manifested itself.

CLINICAL SIGNIFICANCE

In general, paroxysmal forms of auricular fibrillation appear to be an earlier clinical manifestation occurring in less damaged hearts than continuous fibrillation. With few exceptions, the etiology of the two conditions is identical and patients that show recurring paroxysms are to be expected finally to develop continuous fibrillation unless the cause of the arrhythmia is controlled.

Continuous fibrillation does not occur in healthy hearts nor apparently very often in slightly damaged hearts. Paroxysmal or transient fibrillation sometimes occurs in hearts not so seriously damaged and occasionally in apparently healthy hearts that have been subjected to some temporary insult. A case has been reported by Robinson [11] in which transient fibrillation followed the inhalation of hydrogen sulphid, although no evidence of heart disease was discovered. I have observed transient fibrillation in two patients with apparently healthy hearts, one a young man admitted to the University Hospital with virulent acute appendicitis and the other, also a young man, who had first indulged freely in alcoholic beverages of questionable purity and then engaged in friendly wrestling bouts.

The lack of data regarding intermittent fibrillation does not permit speaking with any degree of certainty as to its clinical significance. The highly fibrillary state evidenced by the rapidly recurring paroxysms and the fact that our patient quickly developed continuous fibrillation suggests that the condition of the heart muscle is more closely related to that of continuous fibrillation than the ordinary clinical forms of paroxysmal fibrillation.

SUMMARY

In the case reported, on one examination a condition of fleeting, rapidly recurring paroxysms of auricular fibrillation was found, and on all subsequent examinations, continuous fibrillation. Attention is called to the fact that for the production of this peculiar form of paroxysmal arrhythmia the heart muscle must be not only in a highly fibrillary state, but also at the same time the functional properties of the muscle must be such as to preclude the perpetuation of any of the paroxysms.

11. Robinson, G. C.: Transient Auricular Fibrillation in a Healthy Man Following Hydrogen Sulphid Poisoning, J. A. M. A. **66**:1611 (May 20) 1916.

Auricular extrasystoles were concerned in the onsets of all paroxysms of fibrillation recorded. This is the usual mode of entrance of clinical circus movement, although occasionally it may be initiated by a sinus beat.

Evidence is presented to show that an identical devious pathway was followed by the excitatory process in the various brief paroxysms recorded. This new observation proves that the excitatory process in auricular fibrillation may proceed, for a brief period at least, according to plan and not in a haphazard manner, and is evidence of the fact that there may be but one central or mother wave and not a number of separate fibrillary waves.

The offsets were abrupt and followed by postundulatory pauses of variable duration. It is suggested that the chief factor in determining the position of the succeeding sinus beat is the time of subsidence of the fibrillary excitation in the normal pacemaker, with a relationship similar to that obtaining in the case of auricular extrasystoles.

It is suggested that the form of paroxysmal fibrillation described be called intermittent auricular fibrillation. This condition is apparently closely related to continuous or chronic fibrillation.

ROENTGEN-RAY TREATMENT OF THE SPLEEN IN ASTHMA BRONCHIALE

PRELIMINARY REPORT *

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LYMPHATIC SYSTEM AND ANAPHYLAXIS

The question whether or not bronchial asthma can be influenced by roentgen-ray treatment of the spleen is suggested by the following considerations: There is a definite relationship of the lymphatic system, of which the spleen is one of the most important organs, to anaphylaxis. Symmers [1] holds the view that anaphylaxis is the cause of sudden death in status thymicolymphaticus. The enlargement of the thymus and the lymphatic tissue that is typical for this disease is regarded by Brown [2] as the expression of the abnormally sensitive reaction of the body to foreign proteins. We also know that status thymicolymphaticus is frequently associated with anaphylactic diseases, such as urticaria, asthma, eczema, migraine, hay fever and spastic constipation.[3] On the other hand, in some of the anaphylactic conditions changes in the blood picture are found which resemble very much those occurring in status thymicolymphaticus, namely lymphocytosis and eosinophilia. There is reason to believe that the calcium content of the blood is decreased in anaphylaxis as well as in status thymicolymphaticus,[4] although definite proof is still lacking.

Some authors [5] maintain that the good results of thymus irradiation in thymic asthma [6] are partially due to the stimulation of the lymphatic system exerted by this treatment, and not merely to the mechanical effect of the removal of the thymus tumor. Whether the same reason-

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1. Symmers, D.: Status Lymphaticus, Am. J. M. Sc. **156**:48 (July) 1918.

2. Brown, W. L.: Principles of Internal Secretion, Brit. M. J. **2**:687 (Nov.) 1920.

3. Henke, F.: Der jetzige Stand der Lehre vom Status thymicolymphaticus und seine Beziehungen zu anderen Krankheiten, Deutsch. med. Wchnschr. **46**:1257 (Nov.) 1920.

4. Grove, W. R., and Vines, H. W. C.: Calcium Deficiencies, Their Treatment by Parathyroid, Brit. M. J. **1**:791-795 (May) 1922. Pottenger, F. M.: The Physiologic Basis for the Employment of Calcium in the Treatment of Asthma Paroxysms, Calif. State J. Med. **21**:293-294 (July) 1923. Novak, F. J., and Hollander, A. R.: A New Treatment for Hay-Fever Hyperesthetic Rhinitis, and Bronchial Asthma, Illinois M. J. **45**:285 (April) 1924.

5. Chelmonski, A.: Zur Pathogenese des Asthma Bronchiale, Deutsch. Arch. f. klin. Med. **105**:522, 1912. Klewitz, D. F.: Roentgenbestrahlung bei Asthma Bronchiale, München. med. Wchnschr. **69**:305-306 (March) 1922.

6. Morgan, H. J., and Dachtler, H. W.: Thymic Asthma Successfully Treated by X-Rays, Surg., Gynec. & Obst. **19**:784, 1914.

ing may be applied to the explanation of the great benefit from roentgen-ray treatment of the hilum glands in asthma is a question that has not yet received the necessary attention in literature.

SPLEEN AND ANAPHYLAXIS

Experimental Evidence.—In regard to the part that the spleen takes in anaphylaxis, the work so far reported indicates that the spleen participates in the production of antibodies. This is demonstrated by the following facts: Antibodies are detected in the spleen earlier than in the blood.[7] Antigens have been found localized in the spleen.[8] Cultures of splenic tissue outside the body may produce antibodies in the presence of antigenic substances.[9] The concentration of antibodies in the spleen is greater than in the blood.[10]

In recent years Hektoen [11] showed that removal of the spleen reduces the power of an animal to produce antibodies, whereas irradiation of the spleen seems to increase the antibody titer of the blood. Motohashi [12] confirms the results of Hektoen in regard to splenectomy.

Clinical Evidence.—This idea of Hektoen of stimulating the antibody production by means of roentgen-ray treatment of the spleen was used as the basis for some clinical studies on a small number of asthma patients during the last winter. Most of these patients are definitely improved. Owing to the short time that has elapsed since the beginning of the treatment, the details will be given in a later paper. One case, however, shows such a marked improvement that it justifies a presentation of a detailed account.

Moreover, further support is given to this means of treatment by some German authors,[13] who reported the following results on seventy-one treated cases of bronchial asthma: questionable, ten; negative, seven; good, fifteen; very good, twelve, and splendid, twenty-seven.

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7. Tsurumi, M., and Kohda, K.: The Origin of the Complement Fixating Antibodies, Ztschr. f. Immunitätsforsch. u. exper. Therap. **19**:519-528, 1913.

8. Cary, W. E.: The Fate of Foreign Erythrocytes Introduced into the Blood Stream of the Rabbit, J. Infect. Dis. **17**:432, 1915. Luckhardt, A. B., and Becht, F. C.: The Rôle of the Spleen in the Fixation of Antigen and the Formation of Antibodies, Tr. Chicago Path. Soc. **8**:202, 1911.

9. Carrel, A., and Ingebrigtsen, M.: Antibody Production by Living Tissue Outside the Organism, Compt. rend. Soc. de biol. **72**:220, 1912.

10. Jatta: Ztschr. f. Hyg. u. Infectionskrankh. **33**:185, 1900.

11. Hektoen, L.: Further Observations on the Effects of Roentgenization and Splenectomy upon the Production of Antibodies, J. Infect. Dis. **27**:23-30 (July) 1920.

12. Motohashi, S.: The Effect of Splenectomy upon the Production of Antibodies, J. M. Res. **43**:473 (Aug.-Oct.) 1922.

13. Groedel, F. M., and Lossen, H.: Die Rontgenbehandlung des Asthma bronchiale, reprint of chapter from Salzmann, F.: Die Roentgenbehandlung innerer Krankheiten, Munich, J. F. Lehmann, 1922.

Pohlman,[14] following Groedel's work, states that he treated forty-five cases of asthma, among which only four did not respond to treatment. All others showed distinct improvement. None of the cases of Pohlman or of Groedel has been studied clinically.

REPORT OF CASE

History.—H. D., a white American boy, aged 6½ years, was admitted to the outpatient department of the Children's Hospital, Sept. 22, 1924, on account of asthma. Two brothers and one sister were in perfect health, and no anaphylactic disease could be traced in the family. The child's history recorded pneumonia about two years before admission, and among the usual children's diseases, chickenpox and measles. The boy had severe urticaria three times, the last time one year before. Nearly every fall he had considerable discharge from the nose and was troubled with sneezing.

The first asthma attack dated back four years; the attacks had become more severe and more frequent, recently occurring as often as once in one or two weeks. In the evenings as a usual thing the child suddenly became dyspneic and cyanotic, and many wheezing noises were heard. The attack usually lasted from one to two hours. No vomiting occurred. It could not be found from the history whether food allergy or exposure to any anaphylactogen substance produced the seizures. The boy did not observe any special regulations in his diet; he disliked milk. There was no dog or cat in his home. He did not sleep in a feather bed. In regard to bacterial anaphylaxis, there was no tonsillitis and no sinusitis. A few cavities of the teeth had been noticed during recent months.

Examination.—Physical examination made in an interval between attacks revealed a well nourished, very active boy, who was slightly orthopneic. The skin and mucous membranes showed a good color, no cyanosis being present. A slight dermatographismus was noticeable. A few not sensitive submaxillary glands were felt. The eyes, the ears and the sinuses were negative. The nose showed a considerable watery discharge. The tongue was not coated; the teeth were somewhat ground down and showed a few cavities. The tonsils were not enlarged but were somewhat adherent; no pus could be expressed. The chest suggested a slight barrel shape; the excursions were somewhat embarrassed. The heart dulness was small, 3.5 cm. to the left in the fifth interspace and 0.5 cm. to the right in the third interspace. The sounds were clear though slightly distant; the pulse was regular, full and of normal pressure (112 systolic, 83 diastolic). The lungs showed hyperresonance throughout; the bases descended fairly well; expirium was prolonged, and there were a few bronchitic bruits, especially around the hilum region, but no wheezing sounds. The abdomen, spleen, liver, extremities, genitalia and nervous system did not reveal anything unusual.

Laboratory Findings.—The urine was negative for albumin and sugar and on microscopic examination the red blood cells totaled 4,390,000; the white blood cells, 7,800; hemoglobin, 87 per cent.; polymorphonuclears, 45 per cent.; small lymphocytes, 47 per cent.; large lymphocytes, 4 per cent., and eosinophils, 4 per cent. The Wassermann reaction was negative. The blood calcium was 8.5 mg. The sputum expectorated during an attack and examined in my office showed many eosinophil cells and Charcot-Leyden crystals.

Among the skin tests done we found: milk ++; casein +; eggs, whole, ++, and wheat +. Other tests were negative.

Roentgen-ray examination disclosed a congenital deformity of the third right rib on the sternal portion. The lungs showed extensive bilateral root infiltration with a tendency to extend along the bronchi.

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14. Pohlman, C.: Milzebestrahlung bei Bronchial Asthma, München. med. Wchnschr. **72**:57-58 (Jan.) 1925.

Course of Disease.—September 25, the child received one roentgen-ray treatment of the spleen from Dr. Evans, with the following technic: 6 minutes, 5 milliamperes, 4 mm. Al, 88 kilowatts, 10 inch skin target distance. He was told to observe antianaphylactic diet for two weeks and then no longer to restrict his diet. October 2, he felt very much prostrated, vomited a few times and was slightly dyspneic. October 25, examination of the chest was completely negative. On physical examination, however, no change in the roentgen-ray findings was seen. During the winter months the child had slight bronchitis twice, lasting from two to five days; this cleared up spontaneously. There was not a single attack of asthma after the treatment.

Examination of the chest, May 20, 1925, showed no cyanosis and no orthopnea. Expirium was not prolonged; there was no tympany, and no râles or bruits were heard. The heart dulness was normal. The red blood cells totaled 5,200,000; the white blood cells, 9,400; hemoglobin, 100 per cent.; polymorphonuclears, 71; small lymphocytes, 29; large lymphocytes, 8, and eosinophils, 2. The blood calcium was 15.4. The formerly positive skin tests were negative. The sputum examination was negative for tuberculosis, eosinophils, Curschmann spirals and Leyden crystals. There was no change in the roentgen-ray findings.

COMMENT

The diagnosis asthma bronchiale on an anaphylactic basis does not need any further comment in view of the typical history, of the physical, laboratory and roentgen-ray findings and of the skin tests. The striking feature of this case is the complete cessation of the apparently very severe and frequent asthma attacks during eight months' observation. It is to be noted that the blood calcium rose slightly, the eosinophil cells decreased and the skin tests became negative, while the root infiltration in the roentgenogram did not change on repeated examinations after the treatment. It cannot yet be stated whether the effect of this treatment was due to the psychic influence, as frequently happens in this disease, or whether it conformed with the previously mentioned conception that a stimulation dose of roentgen ray of the spleen may increase the antibody content of the organism. However, similar experiences with other cases seem to indicate that the skin tests become negative within about one week after the treatment. Perhaps the prostration and nausea, which came on seven days later in the foregoing case, may be the main curative factor. Further experimental and clinical studies on this subject are being carried out at present.

SUMMARY

One patient with asthma bronchiale treated with a small dose of roentgen ray over the spleen has been entirely relieved from the clinical manifestations of this disease. The quoted literature, as well as the favorable results obtained on subsequent cases, call for further investigation in this matter.

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THE NONSPECIFIC PROTEIN REACTION *

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A recent series of articles [1] in the ARCHIVES OF INTERNAL MEDICINE merits considerable comment and criticism. Ling attempts to "study comparatively the influence of various nonspecific protein agents on the reactive temperature, . . . on the mobilization of peripheral blood leukocytes, . . . antibodies and enzymes." With the crude mixtures—horse serum, milk, peptone, vaccines, yeast, crotalin—used by him it is obvious that the results obtained cannot be arbitrarily saddled on any one constituent, and also that any attempt to evaluate the results quantitatively is useless.

Ling admits in his article that distilled water produces similar reactions to those produced by the protein mixtures. It was shown in a series of articles [2] in the *American Journal of Physiology* that distilled water, even if it has been sterilized, is capable of producing considerable fever when injected intravenously, and this is because the water had at some time been contaminated by bacteria carried to it by dust in the air or in some other way. These bacteria are able to survive and in fact reproduce in this presumably pure water and may be found in a viable state two months and more after the initial inoculation. They themselves may be killed during sterilization but a soluble product which they have produced during their lifetime and which filters through the Berkefeld candle is heat stable and remains in the sterile water. It is this product, so far unidentified but containing nitrogen, which is responsible for the fevers produced when the waters are injected. The only method so far outlined for removing the fever producing material from water is by distillation. If, however, the distillate is sterilized immediately, it can be kept indefinitely in its pure state. The type and intensity of the fever may be varied in a quantitative manner, according to how much of the bacterial products and what bacterial products are injected.

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1. Ling, C. Y.: Mechanism of Reaction of Nonspecific Protein Agents in Treatment of Disease, I, Influence of Various Agents on Temperature and Leukocyte Counts in Normal Persons and in Rabbits, Arch. Int. Med. **35**:598-608 (May) 1925; II, Influence of Various Agents in Mobilization of Blood Antibodies, ibid. **35**:740-751 (June) 1925.

2. Seibert, F. B., and Mendel, L. B.: Temperature Variations in Rabbits, Am. J. Physiol. **67**:83-89 (Dec.) 1923. Seibert, F. B.: Fever Producing Substance Found in Some Distilled Waters, ibid. **67**:90-104 (Dec.) 1923; Protein Fevers, ibid. **67**:105-23 (Dec.) 1923; Cause of Many Febrile Reactions Following Intravenous Injections, ibid. **71**:621-651 (Feb.) 1925.

Moreover, specific antibodies were produced by immunizing rabbits with one of the contaminated distilled waters to such an extent that serum diluted 1:8,000 agglutinated a strain of bacteria isolated from the water.

In connection with the study of protein fevers, it was shown that casein when prepared in such a manner as to eliminate bacterial contamination did not produce fever when injected into rabbits, whereas all caseins prepared in the usual manner did produce fever. Whether or not it is the protein of the bacteria contaminating the distilled waters that is responsible for the temperature reactions is still an open question, but the presence of nitrogen in the fever producing waters has been demonstrated.

Therefore, in view of these clearly established facts, one cannot evaluate the nonspecific effect of such mixtures as horse serum, milk, peptone, vaccines, yeast, etc., and expect similar results with different preparations of the same substance. The results obtained may possibly be due to contaminating substances and not at all to the agent specified.

Ling's statement that "*Bacillus typhosus*, peptone and market milk gave the most prompt initial temperature reaction, while that produced by market milk seemed to persist longer than that of other agents" may possibly find an interpretation in the fact that different bacteria among the large group that contaminates water vary in just this manner in the reactions produced by them.

Book Reviews

PATHOGENIE DES CALCULS BILIAIRES ET INDICATIONS OPERATOIRES. By THORKILD ROVSING. Price, 20 francs. Paris: Masson & Cie.

This work originally appeared in Danish in 1922, and this French translation is made for the purpose of giving the theories of the author wider publicity. It is frankly a piece of special pleading and as such is ably done, but can hardly be said to be a fair or systematic review of our knowledge of the pathogenesis of gallstones.

The first part of the book is taken up with a critique of the studies of Naunyn and his collaborators on the rôle of infection in the production of calculi. Rovsing is unable to accept any theory that sepsis or biliary stasis are etiologic factors, mainly for the reason that no adequate experimental basis can be offered for this theory. Enterogenous infection is mainly discussed and no mention is made of the work of Rosenow in the production of calculi by the intravenous injection of bacteria.

Aschoff and his school have done a tremendous work on the rôle of cholesterol in stone production. This is reviewed and also found wanting. The word diathesis is used frequently, but the recent discoveries of the chemists in relation to lipoid metabolism are ignored.

Rovsing's theory is that in many toxemias there is a deposition in the liver of minute particles of a calcium compound of bilihumin. These particles are exceedingly irregular and branched and hence readily clump. They can be demonstrated microscopically in the liver and in the bile in pregnancy and in acute toxemias of diverse origin. Most of these pass out into the bowel but some find their way into the gallbladder, where they accumulate in the fundus as they are heavy. As the bile is concentrated in the gallbladder by the absorption of water they are surrounded with deposits of other biliary elements, chiefly cholesterol. There is a network of protein derived from mucus or blood in most stones. Therefore, infection stasis or cholesterol are not factors at all. This theory is elaborately worked out and much evidence in its support produced. However, it cannot be said to be any more definitely proved than the ones discussed earlier in the book.

It is singular that the book treats mostly of stones as isolated phenomena, and not of gallbladder disease as a whole. Perhaps more might be gained from the study of gallbladders than of the stones they contain. McCarthy's work on this subject is not mentioned.

MEDICAMENTS ET MEDICATIONS CARDIAQUES. PAR H. VAQUEZ. Leçons recueillies par M. Theodoresco. Pp. 302. Paris: J. B. Baillière et fils, 1925.

This volume consists of a series of lectures on the treatment of heart disease by Vaquez, designed for his students and edited by Theodoresco. The first half of the volume is given over to a discussion of cardiac remedies, especially digitalis and its allies. It is pleasing to find that the author has seen fit to give as much of the historical background as he has. This is especially true in the case of digitalis. An understanding of what was accomplished by the clinical observations of the earlier investigators should make us all properly humble. This is especially true of Withering, who worked without the recorded experience of others, having only his own observation and deduction to guide him.

After the chapter on the history of digitalis, the drug is taken up in detail, its physiologic action, indications for its use, method of using and dosage. The preparations of strophanthus, especially ouabain, receive more attention

than in American texts. Quinidin is given a full chapter. Under the heading of "Minor Cardiac Remedies" a large number of drugs little used here are considered. The pharmacology does not always coincide with the generally held American and English views, and there is more of therapeutic optimism that is usual in English and American works. The differences in point of view, however, cannot be other than stimulating.

The second half of the volume is taken up with the treatment of cardiac conditions, beginning with a chapter on the hygiene of the cardiac patient, under which are included exercise, diet, and such questions as marriage, military service and anesthesia. Then follow chapters on the treatment of the various cardiac disorders.

It is a decided advantage, in view of the wideness of the field of cardiac knowledge, to have a volume devoted to treatment only. The manner of approach, the clear diction, and the availability afforded by the systematic arrangement add to the value. The author is to well known to make necessary any comment on the scientific worth of the work. It is unfortunate that a reading knowledge of French is not general enough to make books of this kind more generally known and used, or that unedited translations are not more frequent.

LES VAISSEAUX LYMPHATIQUES DU COEUR CHEZ L'HOMME ET CHEZ QUELQUES MAMMIFÈRES. By OTTO C. AAGAARD, Ancien Chef. de Clinique Chirurgicale a la Faculte de Copenhague. Pp. 478; 152 illustrations. Copenhagen: Levin & Munksgaard.

This well written and beautifully illustrated monograph is based partly on the literature and partly on the author's own work. About 200 human hearts were used in this study and comparative observations were made on hearts of other mammals. The lymphatics were rendered visible by the injection method. Many illustrations of historical interest are reproduced.

The monograph is purely anatomic and was presented to the faculty of medicine as a thesis for the degree of doctor of medicine. If this monograph is the type of scholarly requirements for the degree of doctor of medicine in Denmark, that little country has apparently something to teach us in this direction. It is to be regretted that the monograph is so exclusively anatomic. It would have been more valuable if the problems on the significance of the heart lymphatic system in the various conditions of heart disorders also had been considered. It is apparently well established from this work of Aagaard and from that of others that all regions of the heart, including the endocardium and the epicardium, are richly supplied with lymphatics. In man the lymphatic supply is richer in the myocardium of the ventricles than in the myocardium of the auricles.

The publication of the monograph in French renders it less valuable to English speaking physiologists and internists interested in cardiovascular physiology and pathology than it would be if written in English. There is a short résumé in Danish, but no index.